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THE
AMERICAN NATURALIST

VOL. LXI *March–April, 1927* NO. 673

SYMPOSIUM ON GROWTH IN HEALTH AND DISEASE[1]

SOME ASPECTS OF SEXUAL DIFFERENCE IN PRENATAL GROWTH AND DEATH

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EVEN in a field of investigation where little is known it is sometimes advantageous to attempt to place what has there been observed into some sort of relation with accumulating knowledge obtained from other fields—even if in those fields also our information is scant. Exactly this must be done in triplicate here. Prenatal growth, as represented by exact weight relations of the separate organs and systems, is a subject of the future rather than of the past. Prenatal death is clearly a complicated and little understood phenomenon. Sexual difference in either prenatal growth or death is a matter concerning which our information is seriously limited. Nevertheless, perhaps some facts are now available for an estimate of the part played by sexual difference in prenatal growth and death.

These remarks deal with the following general facts and with their consequences. (1) In all placental mammals the early development of male and female embryos

[1] Before the joint session of the sections of medicine and chemistry of the American Association for the Advancement of Science.

must occur in an exclusively *female* environment, namely, the uterus of the mother. (2) The placenta is not a barrier but a filter for at least one important female hormone of the mother into *male* embryos as well as into female ones. (3) The ingress of such maternal hormones produces some well-marked effects on the prenatal growth of certain organs in both male and female embryos; and these effects on such organ growth and differentiation are, in some cases, probably of adverse nature in the case of the male fetus. (4) Still another group of data now indicate that the vitamine and metabolic requirements of male and female are not equal; and, since these requirements are found to be greater in the male, this certainly can also serve to increase the prenatal mortality of the male sex. (5) These adverse changes are probably reflected in the higher prenatal death-rate of the male in some mammals—notably in the human. (6) The currently accepted conclusion—that the higher prenatal death-rate of the male proves that the mammalian male is inherently and constitutionally weaker than the females—is therefore unjustified; since that conclusion rests upon the false assumption that intrauterine life provides an essentially equivalent environment for male and female fetuses.

Some of these several kinds of facts are of very recent development; they have been little considered from any standpoint, and not at all from the point of view of their bearing on the higher prenatal death-rate of the male. A first consideration of the interrelationships of such facts can not hope to be either adequate or satisfactory. Our chief task here is, of course, to present the evidence upon which each of the six preceding summary statements rests.

FETAL ORGANS WHOSE GROWTH IS AFFECTED BY A FEMALE HORMONE FROM THE MOTHER

Bayer (1902) showed that the uterus of the human female fetus is notably enlarged at birth, and that imme-

diately thereafter it undergoes a partial involution or reduction to its normal size. Halban (1904) described a similar puerperal involution in the mammary glands, which were already well known to secrete milk in the new-born human of both sexes. He also found the prostate of males to be enlarged at birth and thereafter to undergo a notable reduction in size. These earlier workers suspected that some product of the mother's ovary was responsible for the prenatal enlargement of these fetal organs at birth. Some time later the work of Steinach (1913) proved that some action or effect or relationship of the ovary is indeed the cause of the mammary enlargement and secretion, since after ovarian transplantation into castrated males these glands became active.

In 1914 Kohn grouped these facts, together with a few others to be mentioned immediately, under the new term "Synkainogenese." Kohn uses this term to describe in embryos of placental mammals all changes from normal development which results directly from the symbiosis of the fetus and mother. Under *Syncainogenesis* is included every disturbance, change or influence of a placental germ which is traceable to a symbiotic union with the gravid mother.

As cases showing such effects he includes the enlarged uterus, the mammae and the prostates already cited. The interesting condition found in the enlarged ovary and testis of the fetal horse was also described. Utilizing the earlier data of Born he notes that high central masses of "interstitial" cells are there present in both ovary and testis, and that in the latter organ seminal tubules almost disappear. In addition Kohn cites the similar cases of the suprarenals and of various changes in the skin and its glands (acne fetalis, etc.). These changes in the skin may here be disregarded, since possibly they are unrelated to the particular *female* hormone which probably is concerned in the other cases under consideration; but the suprarenals are so clearly related to sexuality, and even to certain stages of reproduction, that

they properly belong in the present discussion. Quite recently, Scammon (1926) has supplied some excellent data from a study of the suprarenal growth curve in human fetuses. He says, "the suprarenals, unlike the uterus, show no phase of augmented rate of growth, with respect to the body as a whole, in the latter part of fetal life, preceding their neonatal involution." But his curve for suprarenal growth clearly shows that its rate of growth *throughout* fetal life, or certainly the latter part of it, is entirely beyond that of the period immediately following birth; at which time a very notable decrease of weight occurs. Still more demonstrative is his finding that in "postmature" fetuses—that is, in those overweight and doubtless in part retained beyond term in the uterus—"growth *continues* at approximately the same rate as in the earlier part of the fetal period." This seems to show that the suprarenals of fetuses retained "beyond term" continue to grow; if born "at term" their suprarenals promptly begin to decrease in weight, and indeed lose "approximately one third of the natal weight in the first fortnight after birth." An ovarian influence on this rapid prenatal growth is not suggested by Scammon, but such influence has been pointed out by others (Kohn, Thomas).

Kohn postulated that the ovary supplied a stimulant for these several cases of prenatal growth, and conceived the postnatal involution as a result of a severance of the symbiotic relationship by the act of birth. He further considered most of the above cases as belonging to a type called *physiological* syncainogenesis. The other type, of which a few examples were cited, was called *pathological* syncainogenesis. The levelling of sexual differences was regarded as belonging to the "physiological" type, and male and female were considered as responding in quite the same way to the stimulating substance derived from the mother. It was only later that the identity of this substance could be determined, and evidence for its sex-specificity provided.

Herrmann and Stein (1916; 1920; 1921) obtained facts of a quite different kind which are of importance to the present purpose. They extracted an alcohol-soluble substance from the corpus luteum, and from the placenta, which they injected into rats, rabbits and guinea pigs of various ages—ranging from three weeks after birth to sexual maturity. Their extract was certainly not a pure hormone, but it undoubtedly contained the allegedly specific female hormone of the ovary which has been given such various names (Utero-stimulant; Specifische Ovarialsekret; female sex hormone; follicular hormone, menoform, etc.) by various workers. And they have reported upon the action of this hormone on size changes, and functional and pathological changes in the gonads and other reproductive organs of young male and female animals. Their data therefore permit us to fasten upon an apparently specific hormone produced by the mother and to consider the question whether this hormone is *antagonistic* to the growth and development of the male in early postnatal periods.

They found that injections of this substance did produce increased growth in the genitals and mammae of young females; that such increased growth and secretion was also observed in the Müllerian ducts and mammae of young males; further, that the prostate and vesicula seminalis sometimes enlarge, though this was thought to be rather exceptional, and to result from shorter treatment and lighter dosage. Otherwise, in the young males they report a size *reduction* in the testes (except in very young guinea pigs), the epididymis, the penis, the prostate and in Cowper's glands. Indeed they report degeneration, oedema and other pathological changes in most of these organs. But it must be said that the failure of these workers to give body weights of injected and control animals, and their apparent failure to inject females and males simultaneously with equivalent amounts of the same extracts, leaves some question as to the validity of their conclusions. Some of these findings, however, have

been confirmed by several investigators—notably those concerning increased size of the uterus and mammary glands following the injection of this hormone. Well-known recent American studies on this aspect of the subject are those of Frank and Gustavson (1925) and of Allen and Doisy (1923). But the point of most interest to us here is whether this hormone has *antagonistic* effects upon the genital organs of the male.

On this question Laqueur, Hart and De Jongh (1926) report that injections of this hormone in male rats reduces the size of the testis, and is without effect on the male mammary gland. Steinach (1926) has also reported similar growth-retarding effects in the prostate, penis and vesicula seminalis of young rats from which one testis had been removed. In Steinach's work, however, the number of cases reported is entirely too small, and the body-weight deviations too large, to permit a sound conclusion. In my laboratory, in collaboration with Professor M. Tange, an attempt was made to examine this question of the hormone's antagonism to the testes of young doves. We too probably obtained a reduction of testis size in the injected males; but we knew the *normal* weight and growth-rate of our animals, and found that in this important respect all our males reacted badly to continued injections of a relatively pure preparation obtained from either placenta or from follicular fluid. Our own data do not as yet permit us to declare that this hormone is "antagonistic" to the testes; but it is certain that favorable growth effects, such as were observed in some oviducts of females (Riddle and Tange, 1926), are entirely absent in the males studied by us. The reports of other workers are in agreement on the point that this maternal hormone, reaching the fetus through the placenta or injected in postnatal life, exercises antagonistic growth effects upon *some* of the organs of the male. Further, these reports include not merely adverse growth effects, but in addition some degenerative changes in genital organs of the male. Whether these

changes are or are not capable of affecting the health of the fetus, or of its carriage to term, it must be conceded that they do show that intrauterine life is not equivalent for male and female fetus.[2]

Serological Sex-specific Changes in Mother and Male Fetus

The data of special interest on this subject have been published during the past two years from the Frauenklinik in Halle. Of the several publications we here give definite citations to only four—Sellheim (1924, 1926), Lüttge and Merz (1925, 1926). Using a modification of the Abderhalden reaction Lüttge reports that the blood of the mother shows a pronounced reaction against testis substrate when a male fetus is *in utero*. On the basis of this reaction it is claimed that some sex-specific substance has passed from the fetal to the maternal blood, and also that the sex of the fetus can be thus learned. Sellheim thinks this "antitestis body" formed in the mother is capable of passage from the maternal to the fetal blood; and Lüttge and Merz report, on the basis of similar serological tests, that some specific testis product or products is recognizable in the blood of the fetal male. Thomas (1926) has already pointed out that the substances involved in these reactions are in all probability not of the nature of hormones, since these latter seem not to lead to the formation of antibodies.

On the somewhat related question of spermatotoxins our knowledge is more definite. The several studies of Dittler, Haberlandt and McCartney leave little doubt that

[2] It is well to note that both Kohn (1914) and Thomas (1926) cite the "bird embryo" as an example of development proceeding quite without any influence—syncainogenesis—from the mother. We now know that the maternal hormone discussed above is extractable from ova (yolks), both of birds and of fishes. These embryos also are therefore subject to such influence. In a later communication the writer will cite examples from the pigeon embryo. If the term syncainogenesis is to retain its principal significance we suggest that it must be recognized as applying to all vertebrates, and possibly to many other forms as well.

in various species the absorption of sperm from the vagina, or their parenteral injection, results in the formation of spermatotoxins in the blood of adult females.

Confirmation of the results obtained at Halle is of course highly desirable. Meanwhile it is clear that these early findings indicate that to some extent the mother reacts serologically to a male fetus as to a foreign body. Since this type of reaction is not induced against a female fetus it can not be said that intrauterine environment is equivalent and equally favorable for the male and female fetus. In good alignment with this circumstance Parkes (1924) has presented some evidence that an unusually high proportion of prenatal male deaths occur in older mothers and in later pregnancies. And Fetscher (1924) has utilized an immunization theory to account for the unusual excess of male *births* from *young* mothers—assuming that the mother's blood later becomes more hostile to male-producing sperm. The available evidence for serological changes indicates here, as in the case of its contact with the maternal sex-specific hormone earlier described, that the intrauterine environment is adverse to the male.

SEX-SPECIFIC DIFFERENCES IN NUTRITIONAL REQUIREMENTS

Our third point is concerned with new facts indicating that in certain respects the nutritive requirements for growth and for health are unequal in male and female. These differential requirements concern vitamin B, protein, and metabolic rate. It is true that most of the available data on these particular questions have been obtained on postnatal stages of growth, but there can be little doubt of their applicability to fetal life. Hartwell (1925) concluded that male rats require for their normal growth relatively more vitamine B than do females; and that male rats are first affected by restricted amounts of this vitamine. The rat is the first and only species studied with reference to this point. Parkes

and Drummond (1925) conclude that decreasing the vitamine B supply decreases the proportion of male rats born; they attribute this result to a more harmful effect on the male-producing spermatozoa. Hartwell further concludes that the male rat is more susceptible to the quality of the protein components of its food. Bearing on one or both of these points is an observation of Slonaker and Card (1923) who found that when parent rats were suddenly changed to a restricted diet the proportion of male offspring born "was greatly reduced" (some experiments with malnutrition in mice, however, have given inconstant and inconsistent results). Further, for the human, we have the statistical data showing that in London a higher proportion of boys are born from the well-fed than from the poorer classes. Since these vitamine and protein requirements are apparently greater in the male a higher death-rate of males should result in that fraction of mothers whose nutritional status, in respect to these particular elements, is near the border line.

It is probably true that the male fetus has a higher basal metabolism than that of the female, and this seems to be true for a wide range of organisms, and for the various developmental stages of organisms—a subject rather fully reviewed by the writer in a paper now in press (1926). For the adult human such a sex difference of about 6 per cent. has been found (Harris and Benedict, 1919; Gephart and DuBois, 1916). A similar difference has already been found in children down to a body weight of eleven kilos (Benedict and Talbot, 1915). I was able (1920) to obtain evidence that the minimal oxygen requirement is greater in the male embryos of the pigeon. Without attempting to give further evidence on this point here, we note that a higher metabolism of the male fetus must at least be considered probable; and since this would involve increased nutritional and oxygen demands, this circumstance, like the vitamine and protein requirements just noted, should tend to bring a higher prenatal death-rate on the male side.

Related to these points, and to this entire discussion, is the possibility that many of the organs of internal secretion in mammals do not function during fetal life, but that the fetus is dependent upon the mother for several of these secretions. Thomas (1926) has recently published a volume on this subject, and concludes that there is very little evidence for the normal functioning of the incretory organs during prenatal life. If this is true, or to whatever extent it is true, it may well be that among the incretions of the mother some are better adjusted to, or more adequate for, the female than the male fetus.

In this or another connection the question may be asked whether the "margin of safety" which is usually found in the functional capacity of organs should be capable of making up some of these deficiencies. In general the answer is, no. This is plainly so in the cases of vitamine B and the protein requirement in that fraction of cases where these are at restricted levels in the mother's diet. Again, in all questions concerned with reproduction in the human and other mammals the fact must be faced that the reproductive system is essentially the newest anatomical system of the mammal; and that in many respects it is a very imperfect system of organs whose functioning is deranged with extraordinary ease.

THE HIGHER PRENATAL DEATH-RATE OF MALES AND THE ALLEGED INHERENT WEAKNESS OF THE MALE

It is an observed fact that the prenatal death-rate in the human and some other mammals is notably higher in the males and that the earlier the death *in utero* the higher is the proportion of dead males. Though Parkes (1926) readily states "that the factors causing foetal elimination to differentiate between the sexes are as yet obscure," the conclusion most commonly drawn from these facts by physicians, geneticists and others (Grassl, 1912; Bucura, 1913; Holmes and Goff, 1923; Popenoe, 1926) is that the "male is inherently weaker than the female"—bearing more lethal factors, etc., than does the

female. The argument for this view has been very well and quite simply stated by Popenoe as follows:

> Since the conditions of life in the world, to which the two sexes are subjected, are essentially the same, it is clear that the constitutional weakness of the male is due to internal factors; and since this weakness is manifested most strikingly in the very earliest days of life, months before birth, it seems clear that the cause is to be sought in the constitution of the germ cells. The existing knowledge of the germ-cells suffices to frame a plausible explanation, which seems to satisfy all the requirements, even though it is difficult to prove rigorously. This explanation, which is highly technical in details, is in outline as follows:
>
> It will be recalled that the female possesses two sex (X) chromosomes that are alike, the male two that are different (X and Y). It is supposed that there are a certain number of unfavorable or even lethal factors carried in these sex chromosomes and that the state of normality is dominant over such imperfections, when the two come together in the cell. Therefore a double dose of them is necessary, to give them any effect at all. In the female, then, these unfavorable factors will be felt only when they exist in identical form in the two sex-chromosomes. Since the latter have come into the embryo from different parents, it will rarely occur that the same factors will be found in each one. Hence the female suffers little from them. In the male, on the other hand, any unfavorable factors found in either the X or the Y chromosome are always manifested, since there is no inhibitor in the corresponding chromosome to mask them.
>
> On the basis of this hypothesis, it appears that the very fact which causes a male to be created also causes him to be born with a constitutional handicap which he can not, by any possible method, eliminate.

Now the writer wishes to agree that there is probably a genetic basis for *some part* of the excessive proportion of prenatal male deaths. But, since *a part* of the excess of male deaths must be attributed to the essentially non-genetic conditions already discussed in this paper, these same and similar conditions *may* account for all such excess of male deaths; therefore, *this fact—that an excess of male prenatal deaths is actually found—is one which can not be used at all as an argument for a genetic or inherent weakness of the male embryo, fetus, or individual.* Any demonstration of an innate "constitutional handicap" of the mammalian male must at present rest on another basis than differential frequency of prenatal death in males and females.

Moreover, once questions are raised of "inherent weakness" and of "fitness" of the sexes the answer for

mammals can not be confined to the facts of embryonic and postembryonic growth, health and death. Several different groups of facts relating to female-producing and male-producing (X and Y) *sperms* enter very directly into consideration. One of these kinds of fact is so important to the general purpose of this paper that we mention it—though space limits permit only the briefest statement.

In most mammalian species, including the human, it is the *male-producing* sperm that is the fittest or more efficient in accomplishing the purpose of a sperm—namely, in reaching and fertilizing an egg. At any rate, a full consensus of opinion accepts this as the reason for the large initial excess of males in the sex-ratio of these forms. The alternative would compel the conclusion (against which some facts are known) that a *large excess* of ova fertilized by female-producing sperm *die or disappear at an extremely early age—i.e.,* before sex can be ascertained. But let us note at once that no one has drawn—or is warranted in drawing—the conclusion that the male sex is inherently superior to the female because the sperm which bears the elements normally decisive of development in a male-direction is the superior or efficient one. The best reason for not drawing such a conclusion rests on the circumstance that we are already familiar with the fact that such non-genetic factors as the nature, and particularly the pH, of the secretions encountered by the two kinds of sperm is often decisive of the continued ability of either kind to live or to move, and conceivably they may be differentially affected by any secretion; also, that they probably have unequal capacities of movement. These factors are similar to the non-genetic ones which we have applied in the preceding pages to the intrauterine environment of the growing fetus.

We close this brief discussion of observations in a variety of fields—none of which is adequately explored. The conclusion that the higher prenatal death-rate of

males is due to their inherent weakness is one which can only be drawn on the assumption that intrauterine life provides an essentially equivalent environment for male and female. It is thought that the facts considered here make it clear that such equivalence does not exist. Further, all the three aspects of difference described are adverse to the prenatal growth and health of the male. The observation that the human male death-rate continues relatively high for some postnatal years may mean only that adverse conditions of prenatal life—the sensitive period of highest growth increment and differentiation—can injure without causing immediate death.

Summary

A first attempt is made to examine three groups of newly developed facts concerning intrauterine fetal life in their relation to sexual difference in prenatal death; the result of this examination is applied to the current conclusion that the mammalian and human male is "inherently weaker than the female."

Male and female fetuses are alike forced to undergo their development in a *female* environment provided by the mother. This condition, combined with the further probable fact that maleness (from the Y-sperm stage to adult life) has tendencies, demands and requirements other and greater than those of femaleness, provides unequal chances to male and female for unrestricted growth and health.

An apparently sex-specific hormone (alcohol-soluble; from ovary, placenta, etc.) enters the fetal circulation and is responsible for a special phase of prenatal growth in the uterus of the female; in the mammae and suprarenals (and thyroid?) of both males and females; in the prostate and Müllerian duct system of males. Adverse or antagonistic effects—oedema and degeneration in some cases—have been described in the testes, prostate, penis and epididymis of males.

The serological studies in progress at the Frauenklinik at Halle indicate that the mother's blood reacts to

the fetus as to a foreign body. This "antitestis" body probably enters the fetal blood and apparently induces a reaction in the male fetus. The mother's blood does not appear to react similarly against a female fetus.

The vitamine B, protein and metabolic requirements in postnatal stages are shown to be unequal in males and females, and this difference is probably present during fetal life. Since these requirements are apparently greater in the male this should result in a higher male death-rate in that fraction of mothers whose nutritional status is near the border line.

From the fact that an abnormally high proportion of males is found among the prenatal dead the conclusion is currently drawn by physicians, geneticists and others, that the male is inherently and genetically the weaker sex. This conclusion can be drawn only on the assumption that intrauterine environment is essentially equivalent for male and female. The facts discussed here show that such equivalence does not exist.

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ON THE DISTRIBUTION OF DIFFERENCES IN VITALITY AMONG INDIVIDUALS[1]

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I

IT is proposed to deal in this paper with the general concept of *vitality* and particularly with the concept of *inherent vitality*. Inasmuch as such a statement perhaps has a strange and unfamiliar sound and because the whole point of view which I shall try to develop has certain elements of novelty, we may well start by defining, as rigorously as may be, these concepts which it is proposed to discuss.

However difficult it may be to define life satisfactorily, that is to say rigorously and comprehensively, there is no great practical difficulty in telling whether a particular aggregation of matter, spatially and temporally discrete, is in fact living or not-living, or historically belongs in one or the other of these categories. There are many different ways in which we pragmatically make this discrimination, which I need not stop to list. It is only necessary to suggest their categorical disposition by such words as movement, metabolism, permeability, etc. But all these ways depend ultimately upon the fact that the living organism does things which are different, and does them in ways which are different, from the activities of non-living aggregations of matter (*cf.* Leathes, 1926). In short, the basis of the discrimination between living and not-living material rests upon *events* or *actions* rather than upon ultimate static structures. The essence of life lies in its dynamics and not in its statics.

The considerations just stated imply at once what is an easily observable fact, that there are differences in

[1] From the Institute for Biological Research of the Johns Hopkins University. The substance of this paper was presented in a Symposium on "Growth," before Section N of the American Association for the Advancement of Science, on December 28, 1926.

degree of intensity of the actions which distinguish living from not-living things. These differences may be noted on either a space or a time basis of reference or on a combined base which includes both space and time. Thus the degree of intensity of action may be different in each different individual organism at the same time in the group considered or it may be different at different times in the history of the same individual.

I propose to use the term *vitality,* in a general sense, to mean the degree of intensity of vital actions. Since this is a quantitative concept it is necessary to proceed at once to the consideration of its measurement. In the broadest terms such measurement will always finally depend upon the rate of energy transformation of the organism, within defined limits in respect of space and time.[2] It may be that one will choose to measure the rate of metabolism or the rate of growth or the rate of movement or some other aspect of the energy transformations by the organism. But the point which I wish especially to emphasize, for reasons which will appear later, is that in any and all cases, however they may differ in details, the measurement of vitality must be relative to some defined space-time reference frame. This is obviously so when we measure such things as rates of metabolism, for example, which are differentials in respect to time. It is equally true when we use as a measure of vitality the total duration of life, which certainly may be, indeed so far as I can see, can only be regarded as an integration of all the vital actions of the individual differentiated with respect to time.

It should be clearly understood that "vitality" as here defined has *no relation to or connection with* the concept of "vitalism." It is the generally accepted view of biolo-

[2] After the present paper had been written there came to my desk a paper by Murray (1926) in which the same idea is expressed in the following words (p. 34): "Regarding the organism energetically and dynamically, the amount of energy exchange measures its activity or vitality. Hence, the amount of energy stored plus the amount set free might be used as a criterion of aliveness."

gists that the "activities of living organisms" are completely determined by purely physical and chemical mechanisms and forces, even though it is not possible in the present state of knowledge always to describe these mechanisms or to define these forces rigorously and particularly. The present study fully accepts this physicochemical hypothesis. In fact its whole purpose is to apply to certain biological phenomena some of the methods of reasoning which have in recent years been so fruitful in the domain of physics. But in the discussion which is to follow it is necessary to speak about "the degree of intensity of the activities of living organisms" with some philosophical generality. The single word "vitality" is certainly less cumbersome to use than the detailed definition, and, the sense in which it is to be used having been defined, its use is not less exact or precise.

Now in the energy transformations of the living organism there is involved an irreversible progression which includes three elements, as follows:

A →	B →	C
External Sources of Energy and Non-Living Matter	*The Organism*	*The Product*
(Food. Either chemical compounds of external origin which yield energy and utilizable material when split by the organism (animals), or similar compounds synthesized by the organism itself, with energy derived from light, and subsequently split to yield energy and utilizable material.)	(An aggregation of matter which has the property of autonomously changing A to C, *by virtue of its pattern or organization.*)[3]	(Either (a) heat, (b) work, (c) component matter of the organism, or (d) waste, meaning chemical compounds incapable of yielding energy with economic profit by further splitting.)

[3] This is, of course, Cuvier's "whirlpool" concept of the organism: "La vie est donc un tourbillon plus ou moins rapide, plus ou moins compliqué, dont la direction est constante, et qui entraîne toujours des molécules de mêmes sortes, mais où les molécules individuelles entrent et d'où elles sortent continuellement, de manière que la *forme* du corps vivant lui est plus essentielle que sa *matière*," (1817, p. 13).

The important point in this elementary exposition is expressed in the last clause under B, which is italicized. These seven words are at once a truism and also the statement of one of the most fundamental problems of biology, about which our ignorance is both profound and comprehensively manifold.

What biology has chiefly studied and is at present studying is C, and the transition from B to C, or in other words the becoming of C. One of the difficulties, perhaps the greatest one of all, which interferes with the direct investigation of the *pattern* or *organization*[4] of living things is the circumstance that, generally speaking, the very existence of B depends upon the bond between A and B, represented by the arrow in our scheme, being unbroken. If B is to be observed in action A has to be also in the picture, and in practice it is generally impossible clearly to separate that part of a particular vital event which truly is attributable to the pattern of the organism *per se* from that part in which A, and the transitional stages of A through B to C, are directly involved.

But there are ways in which this difficulty may be avoided. Some years ago there was carried out in my laboratory (Pearl and Parker, 1924; Pearl, 1924) a series

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"Dans les corps vivans chaque partie a sa composition propre et distincte; aucune de leurs molécules ne reste en place; toutes entrent et sortent successivement: la vie est un tourbillon continuel, dont la direction, toute compliquée qu'elle est, demeure constante, ainsi que l'espèce des molécules qui y sont entraînées, mais non les molécules individuelles elles-mêmes. . . . Ainsi la forme de ces corps leur est plus essentielle que leur matière," etc. (1810, pp. 151–152).

Henderson (1913) puts the same idea in these words (pp. 23–24): "Living things preserve, or tend to preserve, an ideal form, while through them flows a steady stream of energy and matter which is ever changing, yet momentarily molded by life; organized, in short."

[4] Perhaps it ought to be stated at this point, so that there may be no misunderstanding, that by pattern or organization I do not mean the anatomy of living things. These words are here used to signify the total dynamic functional-structural integration which is the distinctive attribute of an organism. "Pattern" is the term preferred by Whitehead (1925); "organization" by L. J. Henderson (1917), who follows in this usage the noblest of precedents, that established by Aristotle.

of experiments on the total duration of life of flies (*Drosophila*) in the complete absence of food. The experiments used as material flies which had just emerged from the pupal to the imaginal stage. Great pains were taken to set up the experiments with critical physical precision and accuracy so that the flies should receive no food from external sources, and yet all other conditions of humidity, temperature, etc., should be constant and normal. The net result was to show that, when measured on a relative time base, the distribution of the differences in inherent vitality between the individual flies in the experiment was mathematically substantially identical with the distribution of corresponding differences in nor-

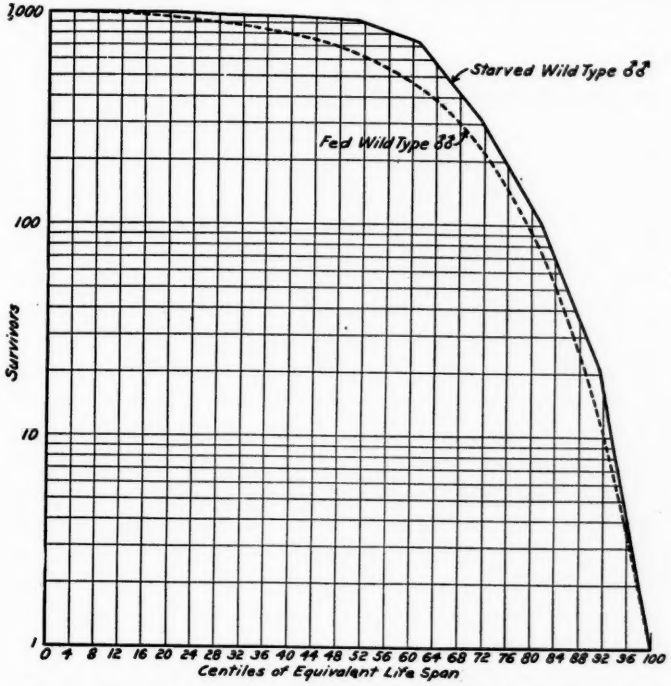
1000
100
10
1
Survivors
Starved Wild Type ♂♂
Fed Wild Type ♂♂
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96 100
Centiles of Equivalent Life Span

FIG. 1. Comparing the survivorship curves on a centile age base of (a) starved wild type ♂♂ (solid line) and (b) fed wild type ♂♂ (broken line). (From Pearl and Parker [1924].)

mally fed flies. This is clearly shown in Fig. 1 copied from the work referred to.

Now in terms of the *schema* already presented these starvation life curves were concerned solely with B, whereas similar experiments with normally fed flies involve both A and B and the transition between them. Why it can be asserted that the starvation experiments dealt solely with B, that is, with differences in the pattern or organization of different individuals, is because whatever nutritive material included in the body, such as cells of the fat body, muscle tissue, etc., which the flies may have utilized before they died of starvation was, after all, *implicate in and an integral part of the total pattern of each individual.* The character, availability and every other characteristic of such endogenous nutritive material as may have been used before death by each individual were all part and parcel of that individual's organic pattern, being as they were solely because that particular fly was just that kind of a fly and no other kind.

This being so, and I see no rational possibility of maintaining that it is not, the result which emerged from the experiment seems to have considerable theoretical interest. It shows that, in *Drosophila* at least, the *form* of the distribution of individual differences in *inherent vitality,* meaning that which is dependent solely upon the organic pattern of the individual, is the same as that of the distribution of general vitality in which both the individual pattern and the external environment play a part. The rôle played by each of these component elements in the total vital situation seems clear in the case of *Drosophila.* It is the environment (food) which determines the absolute values of the coordinates in the space-time reference frame, while it is the organization of the individual in the Aristotelian sense which determines the form or pattern of the event occurring therein.

Another and quite different approach to the direct study of organization can be made through the use of plant seeds as material, taking growth as the index of

vitality rather than total duration of life. It is to some experiments along this line, upon which I have been engaged for some years past, with the able assistance of Miss Agnes L. Allen, that I wish particularly to draw attention on this occasion.

II

The dry seed of a dicotyledonous plant, like a canteloup (*Cucumis melo*) let us say, is a complete but undeveloped individual, containing in the cotyledons, which are morphologically the leaves of the preformed plant which the seed includes, stored nutritive material sufficient to carry the seedling on until the nutrition can be obtained by absorption through the roots and by photosynthesis. The cotyledons and the stored nutriment which they contain are an integral part, and a very important part, of the total organic pattern of the individual. If now we sterilize such a seed, plant it on a medium which contains no food material upon which the roots can draw and keep the whole preparation in the dark, the growth of the etiolated seedling which ensues is an expression of the *inherent vitality* (as defined above) of that individual, since it must draw whatever nutriment it gets from endogenous sources, which are themselves an integral part of the total organic pattern of the individual. Again we shall be able to discuss the B element of our scheme, the pattern or organization of the individual, freed from the disturbing influences of A.

There has been, in the literature, some discussion as to whether etiolated seedlings grown entirely in the dark could carry on, through the intermediacy of "etiolin," some slight carbon dioxide assimilation. This view owed its origin to Ewart (1897). But the work of Irving (1910) would appear to have definitely and finally shown that etiolated shoots have no power of photosynthesis. Furthermore, Willstätter and Stoll (1913) and, more recently, Coward (1924) have demonstrated that "etiolin" consists only of the usual carotinoids of leaves,

xanthophyll and carotin, and so photosynthetic activity could not be expected of it.

The particular actual experiments that I wish to report upon here, which were a part of a much larger series to be discussed later, were carried out in the following way. Samples of two hundred seeds each were taken from a large population of seeds of the canteloup (*Cucumis melo* var.). These samples were drawn at random except that by selection the total weight of each sample, and therefore the average weight per seed, was made nearly the same.

The seeds of each batch were then soaked in 100 cc of sterile distilled water for a period of three hours in the particular series to be reported here. In order to secure complete immersion for exactly the same length of time for each seed the procedure illustrated in Fig. 2 was followed. The distilled water was put in small tanning dishes of the following dimensions: diameter 70 mm, height 50 mm. For each of these dishes a ring of glass

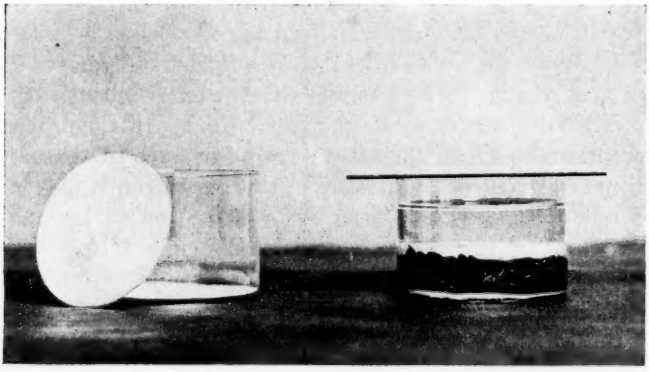

FIG. 2. Showing at left empty dish in which seeds were soaked and cheese cloth ring. The counted seeds are placed on a filter paper slightly larger than the diameter of the dish, and the cheese cloth ring laid over them. Then the filter paper and ring, with seeds between, are carefully thrust down into the dish of water. The appearance of the seeds while soaking is shown on the right hand side where the edge of the filter paper is seen at the bottom, above it the soaking seeds, and above them the cheese cloth piston ring.

rod was made by the glassblower. Over the ring was stretched a piece of cheese-cloth like a drum head, held tight by sewing the edges of the cloth around the ring. The size of the ring was so calculated that, with the cloth on, it fitted the dish as a piston fits a cylinder. By a simple manipulation the counted seeds can be put under the cheese-cloth ring and thus held totally immersed, and each for the same length of time.

After the seeds had been soaked for three hours they were removed, drained of adhering water and placed on the surface of an agar plate, as shown in Fig. 3.

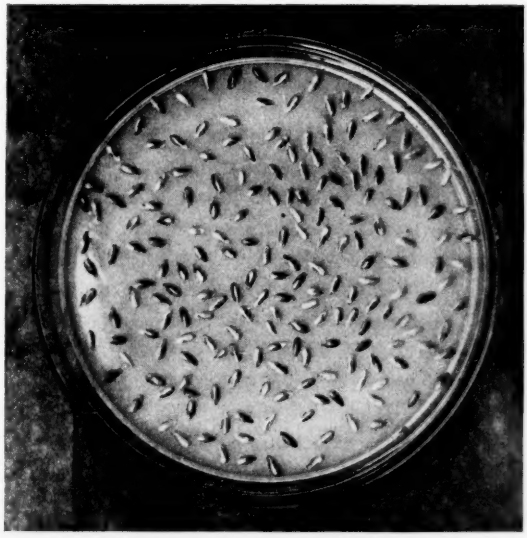

FIG. 3. Photograph of 200 seeds on agar plate.

The agar plates were poured in Pyrex glass pie plates 21.5 cm in diameter. 350 cc of 1.5 per cent. agar, made with sterilized distilled water, the whole resterilized in the making, was poured in each pie plate. The plates after pouring were covered with flat glass plates and left over night before sowing the seeds on them, in order for the agar to set in a firm jelly.

After the seeds were distributed on the plates, two hundred to each plate, and again covered with flat glass plates to prevent evaporation and to protect the preparation from contamination, they were placed in an electric incubator running at 30° C. The incubator was completely dark inside.

From this point on the procedure was as follows: The plates were examined at frequent intervals. Whenever any sprouted seeds were observed on a plate they were counted, and then very gently and quickly removed to growing dishes, in which 100 cc of 1.5 per cent. sterile agar made with sterile distilled water had been previously poured and set. No more than twenty-five sprouted seeds were put in each such growing dish. If more than this number were ready to come off the plate at any given observation time, twenty-five were counted into the first dish, and the remainder, if less than twenty-five in number, put into a second dish, and so on. These growing dishes were then covered and immediately put back into the incubator, and the seedlings in them were allowed to grow in the dark at 30° exactly forty-eight hours. At the end of the forty-eight-hour period the dishes were removed from the incubator. Each seedling was then carefully removed from the agar and at once separated with a sharp scalpel into its three morphological components, (a) cotyledons, (b) stem and (c) root. These parts were then put separately into vials of 5 per cent. formalin, in order to preserve them for subsequent weighing. It was necessary to hold them in this way, because the pressure of the experimental work did not permit of doing the fresh weighing at the time.

After an experimental run was finished the material was taken from the vials, all adhering moisture removed by blotting with filter paper, and the parts then weighed to the nearest one tenth of a milligram. The material was then returned to the formalin vials and passed on to the consulting chemist of this institute, Dr. W. B. D. Penniman, who then in his laboratory dried the material

at 98° C. and determined the dry weights of each lot to the nearest one tenth of a milligram.

Reviewing the whole procedure it is seen that what we did was to let the seeds germinate until there was a visible sprout averaging approximately 1 mm long, keeping exact record of the time it took to do it. These sprouted seedlings were then transferred to a fresh agar surface and allowed to grow exactly forty-eight hours in the dark, and then weighed by parts. The only important sources of error in the experiment were these:

(1) Even with frequent observations there was some variation in the length of the sprouts at the time the seedlings were transferred from the plate to the growing dish to observe the forty-eight-hour growth. This variation was not large, however, and was insignificant in comparison with the total growth obtained. (2) The weights after preservation in formalin were not true fresh weights. In the way the experiment was planned, for quite another object than the present one, it was impossible to take the fresh weights at the time. A special investigation of the point showed that by storage in 5 per cent. formalin there was a loss of 12.7 per cent. in weight in the case of the cotyledons, 10.2 per cent. in case of stems, and 13.6 per cent. in case of roots. Obviously the formalin weights recorded can not be substituted for true fresh weights. But in the present study, and in the other work for which the experiments were planned, *absolute* weights were unimportant. The concern was with *relative* weights of different batches. We have found no evidence that relative weights are altered by the formalin treatment. Furthermore we have found no alteration of dry weights, either absolute or relative, by this procedure. (3) The agar substrate on which the seedlings grew was a high grade of bacteriological agar, which is of course mainly cellulose. But upon analysis it was found to contain 3.37 per cent. of mineral matter by weight, of which 3.12 per cent. was acid soluble. This means that the whole of the agar jelly in each growing

dish contained .00158 gram of acid soluble mineral matter. Assuming that all the acid soluble material was also water soluble and capable of being absorbed by the roots of the seedlings, if the twenty-five plants in a growing dish had taken out *all* of the soluble mineral matter in the dish, each seedling would have got only 0.00006 gram of such matter. But such an assumption greatly overstates the possibility. So I think we may fairly conclude that only a trace of possibly useful mineral matter could have been of exogenous origin in the experiment.

III

Returning now to the main thread of our discourse, we have provided, by the experimental procedure described, measurements of the initial forty-eight hours' growth of canteloup seedlings, under conditions controlled and limited with physical precision so that the entire food material for the growth must be derived from endogenous sources, which are themselves an integral part of the organic pattern of the individual, except for the possibility of a trace of soluble mineral salts which may have been brought into the plants through the roots from the agar substrate. It has been shown that this possible exogenous material is insufficient in amount to be in any appreciable degree significant in the results.

What happened in the experiment, of course, was that some seeds germinated earlier than others, and were, in consequence, removed from the sprouting plates to the growing dishes earlier. The record of germination of a typical series is given in Table 1. On account of limitations of time I shall discuss here only this typical Series I. The experiments on which the conclusions reached in this paper have been reached have been repeated and confirmed many times in my laboratory, with a variety of minor modifications in the technique. A considerable amount of work has already been done on the experimental modifications of inherent vitality or the innate pattern of the organism. All these results will be re-

ported in detail elsewhere. On the present occasion it seems wise to make the discussion of what is at best a complicated matter as clear as possible by confining our attention to a single typical series of experimental results.

TABLE 1

GERMINATION RECORDS. SERIES I

Hours on plate	Seeds germinated	Per cent. germinated	Total number germinated	Cumulated per cent. germinated
26.1	57	28.5	57	28.5
31.2	48	24.0	105	52.5
43.3	66	33.0	171	85.5
50.7	9	4.5	180	90.0
68.8	3	1.5	183	91.5
95.0	5	2.5	188	94.0
118.6	4	2.0	192	96.0
142.7	3	1.5	195	97.5
166.0	0	0	195	97.5

It is evident that the final percentage of germination attained was high. This is a reflection of the extraordinary usefulness of the agar plate technique in studying germination. We have tried many other procedures for the accurate study of germination, but have found none to compare with the agar plate method for accuracy, constancy and high absolute germination.

The inherent vitality of a seed, when measured by growth, is clearly a function of two observed elements, namely:

(1) The *amount* of new substance added as the result of the growth, expressible among other ways as the weight, fresh or dry, of the stem and root together (*i.e.,* rest of the plant after removal of the cotyledons).

(2) The *time* the individual took to accomplish the amount of growth specified under 1.

In the present experiments the time during which the seedling was allowed to grow after it had germinated was made constant at forty-eight hours for each individual. But, as is clearly shown in Table 1, the time taken to

reach germination under the uniform and constant environmental conditions of the experiment was quite different for different individual seeds. But this duration interval from the time when the seeds were put on the plate till they showed visible germination and were transferred to the dishes is clearly a part of the expression of the inherent vitality of the seeds. Those seeds that use a short time in reaching this stage of growth are exhibiting a more rapid rate of action, or a more intense vital activity per unit of time, than those which take a long time to reach the stage of visible sprouting.

The results of the experiments are exhibited in Table 2, which includes the following items:

(1) The absolute time (number of hours) the seeds were on the germinating plate before removal to the growing dishes; that is, before visible germination.

(2) The relative time spent by the seeds on the plates before germination, got by reducing the figures in column 1 to percentages of the total interval up to the time when the last seeds in the lot ever to germinate had done so.

(3) The total number of sprouted-seed-hours exposed to risk of growth. This is an actuarial expression which properly combines into one figure the space-time elements which are necessarily and inseparably connected in any quantitative expression of growth. It is got by multiplying the number of hours spent by the sprouted seeds on plate and dish by the number of such seeds.

(4) The absolute weight in grams of the stems and roots together, attained at the end of the forty-eight-hour stay in the growing dishes, per ten thousand sprouted-seed-hours exposed to risk of growing. There are two columns of these absolute weights: (a) the formalin "fresh" weights, and (b) the dry weights.

(5) The relative attained weights per ten thousand sprouted-seed-hours, got by transforming the absolute weights of columns 4a and 4b to relative figures, on the basis of taking the mean of the first four observed weights in each series as equal to 1. The reason for

making this simple transformation will appear as we proceed.

TABLE 2

GROWTH RECORDS. SERIES I

Hours on plate 1	Relative time on plate in per cent. 2	Sprouted-seed-hours exposed to risk of growth 3	Absolute weight of stems and roots in grams per 10,000 sprouted-seed-hours exposed		Relative weight per 10,000 sprouted-seed-hours	
			Formalin "fresh" 4a	Dry 4b	Formalin "fresh" 5a	Dry 5b
26.1	15.7	4233.6	5.526	0.201	1.00	0.99
31.2	18.8	3792.1	6.861	0.256	1.24	1.26
43.3	26.1	6062.3	5.427	0.203	0.98	1.00
50.7	30.6	891.4	4.230	0.154	0.79	0.76
68.8	41.4	350.0	5.117	0.200	1.00	0.98
95.0	57.2	715.6	2.135	0.085	0.39	0.42
118.6	71.5	667.1	1.127	0.062	0.20	0.30
142.7	85.9	572.0	1.163	0.041	0.21	0.20

IV

There are two immediate conclusions of some importance which flow from the experimental data set forth in Table 2.

The first is that, within the limits of the experiments discussed, growth is a self-consistent measure of inherent vitality. The seeds which took the longest time in germinating made the least growth in a constant time interval thereafter. Except for minor fluctuation presumably due to random "errors" in the experimental procedure, this relationship is consistent throughout the table.

The second result is that the measurement of inherent vitality by means of the time rate of growth, as in the experiments here described, leads to substantially the same distribution of differences among individuals in respect of this attribute of the organism that is found if inherent vitality is measured in terms of total duration of life, as in the *Drosophila* experiments under conditions of starvation. This fact is demonstrated in Fig. 4.

In this diagram two lines are plotted. The solid line is the p_x line calculated from the data of Table 1, in the paper by Pearl and Parker (1924) cited above, for starved wild type male flies in bottles of initial density 50. The function

$$p_x = 1 - q_x,$$

gives the probability of living through a period of 6 hours beginning at age x. The abscissae are expressed in Fig. 4 as centiles of the total adult or imaginal life span under conditions of complete starvation, rather than in hours.

The broken line of Fig. 4 is the graph of column 5b of Table 2, plotted against the abscissal points given in column 2 of the same table. The ordinates express the mean relative growth of the canteloup seedlings, per ten thousand sprouted-seed-hours exposed to risk of growing, over a constant period of forty-eight hours, at the indicated relative times of starting visible growth.

There can be no doubt as to the substantial identity of the two distributions shown in Fig. 4. The seedling curve

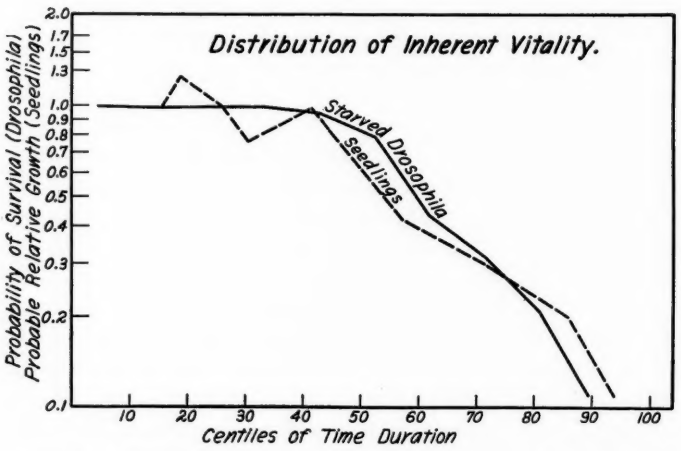

FIG. 4. Comparing the distribution of inherent vitality of *Drosophila*, measured by total duration of life (solid line), with that of canteloup seedlings, measured by relative growth (dash line), both without exogenous food.

starts later than the *Drosophila* curve because seedling growth was not measured until it became visible after germination. The seedling curve is irregular in its early part, because the experiments from which the data here presented were derived were planned for an entirely different purpose from that to which they are here applied. For the original purpose of the experiments it was not essential that all the seeds should come off the plates at precisely the same stage of attained growth. There was some variation in this matter which reflects itself in the fluctuation at the beginning of the curve.

But the broad fact seems to be demonstrated that differences in inherent vitality as defined in this paper—the activity of living things which is an expression solely of their innate pattern or organization—have the same type of distribution among individuals, whether this attribute of the organism is measured by total duration of life or by rate of growth. Furthermore, the form of the distribution of inherent vitality is substantially the same in such widely different living things as an insect and a cucurbitaceous plant. The experiments on flies and on seeds which furnish the data for the present discussion were made at different times three years apart. In neither case was there any thought of their results being used in support of the ideas upon which the present paper is based. It is not without a certain impressiveness that two such totally independent pieces of research should, under the influence of a synthesizing idea of much later date, yield such a concordant picture as is shown in Fig. 4.

It is entirely certain that in the experiments here recounted, both those with *Drosophila* and those with seedlings, the observed differences between individuals in respect of vital activity can not possibly be accounted for by differences in the environmental forces acting upon the individuals. They represent, on the contrary, innate differences in the action-pattern of the living individuals themselves. The reason why this assertion can be so

positively made, apart from and beyond the theoretical reasons set forth at the beginning of this paper, is that the environmental conditions surrounding and acting upon each individual were made identical by the most scrupulous exactitude in the experimental procedure. The *possible* differences in the environmental conditions acting upon the different individuals in the experiments were of the order of infinitesimals, in comparison with the large differences in the resulting vital activities of the several individuals.

Summarizing, the following points appear to have been established:

(1) That the distribution of individual differences in inherent vitality is of the same form as that of differences of total vitality, when vitality is measured by total duration of life under conditions (a) of starvation and (b) of normal feeding, temperature and other environmental conditions being the same in the two cases.

(2) That the distribution of individual differences in inherent vitality is of the same form when measured as the integrated time variable total duration of life, or as the differential time variable, rate of growth.

(3) That the distribution of individual differences in inherent vitality is of the same form in such widely different organisms as *Drosophila melanogaster* and *Cucumis melo*.

These facts would seem to indicate that in the concept of inherent vitality here developed we are dealing with a matter of real biological importance.

The direct approach to the study of the action-pattern of organisms, to which this paper is offered as a contribution, opens a vista of entertaining possibilities in biological research. We are busily engaged in my laboratory at the present time in exploring some of these possibilities and hope to be able to report upon them in the not too distant future.

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THE FUNCTIONAL SIGNIFICANCE OF THE SUPRARENAL CORTEX[1]

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IT has long been known that complete removal of the suprarenal glands of mammals is soon followed by death of the animal. For example, untreated cats rarely survive bilateral epinephrectomy for more than three or four days—the average survival period being about sixty hours. Untreated dogs live about six and one half days on the average. Species differ in regard to the life span following gland removal, but all observers who have worked with cats, dogs and guinea pigs agree that destruction of the suprarenals is incompatible with life. This holds true for humans also, since Addison's disease almost invariably terminates fatally. Because of the necessity of functional adrenal tissue for life, these glands have long excited the interest of experimentalists, but despite the sacrifice of many animals and a vast amount of labor, the cause of death following adrenal ablation is unknown.

The problem of the functional significance of the adrenals is rendered difficult by the fact that they really consist of two separate and distinct structures. The suprarenal of mammals consists of an outer shell or cortex and a central core or medulla. These two portions of the mammalian gland are separate and distinct in the Selachians. During the course of vertebrate evolution the two glandular portions have united—the interrenal body of the primitive vertebrates forming the cortex and the paired adrenal structures becoming the medulla of the suprarenal complex of higher vertebrates. Even in mammalian ontogeny the two parts of the suprarenal

[1] Symposium before a joint session of the sections of medicine and chemistry of the American Association for the Advancement of Science, Philadelphia, December, 1926.

arise separately, and only fairly late in development do they unite.

Thus comparative anatomy and embryology show clearly that the suprarenal of mammals is a complex of two glands, each probably serving a different function. When death ensues following adrenal removal, the question immediately arises: Which portion is responsible, or are both parts, cortex and medulla, equally involved? Does the cortex participate with the medulla in the synthesis of adrenaline, or does it have an entirely different function? In order to answer these questions it is first necessary to devise means for separating the cortex from the medulla—not an easy thing to accomplish, as attested by the fact that so few workers have attempted the operation.

A vast literature has grown up concerned with the medulla and its functions, but very few papers are to be found dealing solely with the cortex. This is doubtless due to the discovery and identification of adrenaline as the active principle of the medulla. However, survey of the meager literature on the cortical portion of the suprarenal reveals some significant facts, all of which point to the conclusion that it is the cortical portion of the suprarenal which is essential for life. The adrenal medulla may, and probably does, play a very important rôle in the organism, but it is not essential for the maintenance of life.

The researches of Biedl (1913), Wheeler and Vincent (1917), Wislocki and Crowe (1924), Houssay and Lewis (1923), and Zwemer (1924–26) in our laboratory, have shown beyond question that the cortex is vital for life, since destruction of the medulla is without demonstrable effect, whereas severe injury to or removal of the cortex results in typical symptoms of adrenal insufficiency terminating fatally.

Biedl (1913) was the first to call attention to the significance of the cortex for the maintenance of life. He removed the interrenal body from twelve specimens of

Scyllium. Two animals died within ten days and autopsy failed to reveal any remnants of interrenal tissue. The other ten animals survived and when later killed it was found that extirpation had been incomplete. In later experiments performed upon thirty-two animals (Raia) all the interrenal tissue was removed from twenty-seven. The animals died within a short time exhibiting typical symptoms.

Wheeler and Vincent (1917) in a series of operations on thirty dogs, twenty-two cats and four rabbits, succeeded in removing one and one half adrenal and in destroying the medullary portion of the remaining half by cautery. Three weeks later the cauterized half gland was removed, post-mortem, and examined for chromaffine tissue. Several cases showed none to be present.

Houssay and Lewis (1923), working on dogs, curetted the medulla from one gland and extirpated the other, after the lapse of a week or ten days. Twenty-five animals were used and most of them survived the operative procedure. Only two animals were brought to a third operation in which the curetted cortical gland was removed. The two dogs lived twenty-four and twenty-six hours after extirpation of the cortical remnant which had kept them alive for over two hundred days.

Wislocki and Crowe (1924) also worked with dogs. They employed two animals, removing one adrenal and two thirds of the other and cauterizing the medulla of that portion left in the animal. In addition they removed the abdominal chromaffine body. The dogs survived in excellent condition until the surgically produced cortical remnant was removed.

Zwemer (1924–26), working with the writer, and using cats as experimental material, has recently reported a detailed investigation of the survival value of the suprarenal cortex. His results are as follows:

(1) Unilateral extirpation of the adrenals has no ill effect on the animal.

(2) Cats deprived of both adrenals, in two stages, with an interval of five to ten days between operations, sur-

vive about fifty-three hours on the average, the extremes being twenty-six hours and one hundred eleven hours. (In a more recent series of experiments, the present writer found the average survival period for cats so operated to be sixty hours if the animals are not forcibly fed milk or other liquid when they first refuse food. If milk or liquid is forced, the life-span is greatly lengthened and the animal may survive for as long as seven to twelve days. See Corey, 1926, for detailed account of similar experiments.)

(3) Animals retaining only the cortex of one adrenal with undisturbed blood supply survive indefinitely.

(4) Removal of this surgically produced cortical gland causes death in from one to eight days. Histological examination showed that many of the glands were composed only of cortical tissue.

(5) Transplants of the adrenal cortex prolonged life in bilaterally epinephrectomized cats for an average of six and one half days but degeneration of the grafts eventually caused death.

(6) The conclusion is drawn that the cortex is the portion of the adrenal complex essential for life in cats.

Recently Jaffe (1926) has reported successful grafting of the adrenal cortex in rats and guinea pigs. The latter animals rarely survive bilateral epinephrectomy for more than a few days, but if grafted with cortical tissue they survive for long periods.

During the progress of Dr. Zwemer's work, the writer was carrying on an intensive study of the functional significance of the cortex and we had ample opportunity to compare observations. Both Zwemer and myself observed a few cases of cats surviving complete adrenal removal. Autopsy generally revealed the presence of accessory cortical tissue.

Accessory glands are relatively rare in cats. In our series of two hundred animals only a few cases have been found. The percentage may be higher, since accessories were searched for only in those cats surviving double

operation. Animals dying with typical symptoms were judged not to have functional accessories.

Our experience leads us to believe that any cat surviving bilateral adrenal removal possesses accessory cortical glands. In all but one of our cases the accessory tissue consisted solely of cortex. Animals with accessories generally show some symptoms of adrenal insufficiency for several days after the second operation, the onset of symptoms usually being about thirty to forty-five hours after operation. The symptoms, such as weakness and lethargy, may persist for ten days or so and only gradually disappear, although several of the animals exhibited no signs whatever of adrenal insufficiency. Recently the writer was successful in finding, and removing, an accessory cortical gland from a bilaterally operated cat that had survived twenty days and had fully recovered. The animal lived eighty-one hours after the operation, and was normal for the first forty-four hours, before typical adrenal insufficiency symptoms developed. Seven hours before death the blood was taken and tested. CO_2 capacity was 22.4 cc., CO_2 content 16.7, blood sugar 66 mgm., inorganic phosphorus 10.6 mgm. per 100 cc.

Animal species seem to differ considerably in regard to the frequency with which accessory cortical bodies are found. For example, guinea pigs, cats and dogs rarely possess such glands, whereas they are common in rabbits and very common in rats. Data on other species are lacking. The occurrence of accessories is not difficult to understand in the light of the embryological origin and development of the suprarenal cortex.

Continued observation of bilaterally operated cats through all stages of adrenal insufficiency revealed peculiar changes in respiration of those animals showing typical symptoms. Despite the fact that cats showing symptoms are lethargic, drowsy and take little interest in their surroundings, they show increased rate and depth of respiration, especially the latter. When such

cats are disturbed and forced to walk about, the least exertion seems to tire them and they sink down as if exhausted, breathing rapidly and deeply. As symptoms progress, the respiration is accelerated, and in the terminal stages dyspnea and hyperpnea are present.

It occurred to the writer that the animals exhibited symptoms of acid intoxication. In order to test the idea the cooperation of Miss A. J. Eisenmann, of the Department of Internal Medicine, Yale University, was enlisted, and a study made of the acid-base equilibrium of unilaterally and bilaterally operated animals (Swingle and Eisenmann, 1926). For a detailed account of the experiments the reader is referred to the original paper.

Serum protein, serum carbon-dioxide, serum chloride, inorganic phosphorus, total base and pH were determined. The acid values of protein, bicarbonate, chloride and phosphorus were calculated. Total acid was taken to be the sum of all the determined acids. Organic acid was calculated by subtracting total acid from total base and includes sulphate ion.

The determinations were made on unilaterally operated animals (normals) and repeated on the same animal at varying times following the onset of symptoms. Certain differences from the normals are grossly evident in the cats exhibiting marked symptoms of adrenal insufficiency.

(1) The tension of carbon-dioxide always drops.
(2) The serum carbon-dioxide content always drops.
(3) The carbon-dioxide combining power of the serum is markedly lowered.
(4) There is always a fall in pH a few hours before death.
(5) Proteins rise.
(6) There is usually a marked rise in inorganic phosphorus.
(7) Total acid always diminishes.

The drop in total acid is almost completely at the expense of bicarbonate. The fall in bicarbonate concentra-

tion and carbon-dioxide tension can not be due to overventilation, because the latter would result in an increase of pH. In these experiments pH remains practically unchanged for some days following onset of symptoms and falls rapidly a few hours before death. The fall in pH which finally occurs indicates that the bicarbonate reduction is due to a non-volatile acidosis for which the respiratory mechanism has not compensated. Chloride concentration was not consistently altered and therefore can not be the cause of the carbon-dioxide change. Nor can increase in protein concentration be responsible because it is offset by the decreased base-binding power of protein at the lower pH. The fall in bicarbonate can not be occasioned to any considerable extent by the rise in phosphorus, which although marked never exceeds two millimols, while the carbon-dioxide falls six to ten millimols.

Increase in organic acid is the one change of sufficient magnitude to be responsible for the bicarbonate fall. The nature of the organic acid or acids is unknown. Ketosis is not a factor, since repeated determinations made on the blood of comatose cats dying of adrenal insufficiency showed the presence of less than 3 mgm. of acetone per 100 cc. of blood.

The fall in pH, carbon-dioxide tension, content and combining power, diminution in serum bicarbonate and total acid indicates that the bilaterally epinephrectomized animals showing marked symptoms of adrenal insufficiency are suffering from an uncompensated non-volatile acidosis or acid intoxication. This seems to be due to an increase of phosphoric and undetermined organic acids.

Since this was written, the writer has completed another series of experiments, designed to show that long surviving double operated animals do not differ from those dying between forty-five and sixty hours after the second operation. The changes in the alkali reserve are highly significant. A few of the protocols (abbreviated) are included.

PROTOCOL ONE

Cat 341. Adult male. Right gland removed November 29. Bled December 2. CO_2 capacity, 39.3 cc.; CO_2 content, 34.1 cc.; blood sugar, 101 mgm. Left gland removed December 3, 11 A. M. December 4, drank milk; normal. December 5, normal, drank milk and ate meat, 9 A. M. 6 P. M., refused food. 11 P. M., animal lethargic and weak in hind limbs. 2 A. M., December 6, cat "droopy" and seemed weak. Bled. CO_2 capacity, 29.1 cc.; CO_2 content, 19.4 cc.; blood sugar, 80 mgm. 8 A. M., December 7, cat prostrate and verging on coma. Breathing rapidly—37 per minute. Bled. CO_2 capacity, 17 cc.; CO_2 content, 10.8 cc.; pH, 7.26 (electrometric); blood sugar, 55 mgm.; phosphorus, 12 mgm. Animal died ten minutes after bleeding. Total survival period—ninety-three hours. Autopsy revealed nothing unusual in gastrointestinal tract. Congestion not marked. No blood. Some congestion of pancreas and spleen.

PROTOCOL TWO

Cat 344. Adult female. Right gland removed December 1. December 4, bled. CO_2 capacity, 40.1 cc.; CO_2 content, 36 cc.; blood sugar, 110 mgm. Left adrenal removed December 10, 2 P. M. December 11 and 12, cat normal, ate. 9 P. M., December 12, cat refused food. December 13, animal quiet and refused food. 10 P. M., animal drowsy, lethargic and slightly weak in hind legs. Bled. CO_2 capacity, 30.1 cc. December 14, 9 A. M., cat weak, staggered when walking. Respiration deep. Bled 4 P. M. CO_2 capacity, 28.1 cc.; CO_2 content, 24 cc.; pH, 7.27 (electrometrically). 11 P. M., December 14, cat prostrate and verging on coma. Respiration rapid—40 per minute. Bled. CO_2 capacity, 21.2 cc.; CO_2 content, 14.5 cc.; pH, 7.21 (electrometrically); blood sugar, 65 mgm.; phosphorus, 11.1 mgm. per 100 cc. Cat died 11:15 P. M., December 14. Total survival period—105 hours. Autopsy showed nothing unusual in the gastrointestinal tract.

PROTOCOL THREE

Cat 346. Adult male. Right gland removed December 6. Bled December 9. CO_2 capacity, 44.2 cc.; CO_2 content, 38.6; blood sugar, 109 mgm. Left adrenal removed December 11, 4 P. M. Cat showed no symptoms on December 12 or 13. 9 A. M., December 14, cat lethargic and refused food. Bled. CO_2 capacity, 32 cc.; CO_2 content, 26.5 cc.; blood sugar, 88 mgm. 10 P. M., cat about the same; breathing deeply. December 15, 9 A. M., cat weak, lethargic and breathing fairly rapidly and deeply. Bled. CO_2 capacity, 23.2 cc.; CO_2 content, 15.9 cc.; blood sugar, 71 mgm.; phosphorus, 10 mgm. per 100 cc.; pH, 7.35 (electrometrically). Animal died December 15 at 11 P. M. Total survival period—103 hours. Autopsy showed no unusual change in the gastrointestinal tract.

PROTOCOL FOUR

Cat 351. Adult male. Right gland removed December 9. Bled December 12. CO_2 capacity, 41.2 cc.; CO_2 content, 37.6 cc. Left gland removed December 13, 10 A. M. December 14 and 15, cat normal. December 16, refused food. Forcibly fed milk, 100 cc. a day. December 17, forcibly fed

milk. December 18, 11 A. M., cat very lethargic and "droopy." Bled. CO_2 capacity, 23.5 cc.; CO_2 content, 13.3 cc.; blood sugar, 64 mgm. Cat drank a little milk five minutes before being bled. Cat restless and walked about at 5:40 P. M. Bled. CO_2 capacity, 20.8 cc.; CO_2 content, 13.1 cc. December 19, cat died at 9 A. M. Total survival period—143 hours. Phosphorus, 12.5 mgm. five minutes before death. Autopsy revealed no pathological changes in the gastrointestinal tract except two small gastric ulcers.

PROTOCOL FIVE

Cat 356. Adult male. Right gland removed December 10. Bled December 12. CO_2 capacity, 40.1 cc.; CO_2 content, 38.6 cc.; blood sugar, 104 mgm. Left adrenal removed December 13, 9 A. M. December 14, no symptoms. December 15, no symptoms. December 16, 10 A. M., cat refused food. Lethargic and "droopy." December 17, 11 A. M., cat exhibited marked symptoms. Respiration rapid and deep—30 per minute. Bled. CO_2 capacity, 20.1 cc.; CO_2 content, 15.4 cc.; blood sugar, 64 mgm.; phosphorus, 10.6 mgm. per 100 cc. Cat died five minutes after bleeding. Autopsy showed no changes in the gastrointestinal tract. Spleen and pancreas somewhat congested. Total survival period—98 hours.

The marked fall in the alkali reserve following bilateral extirpation is grossly evident from the data presented in the protocols. The phenomenon is not a terminal one heralding approaching death, but first becomes manifest with the early appearance of adrenal insufficiency symptoms. A progressive fall in bicarbonate accompanies the increased severity of symptoms.

It is the opinion of the writer that one of the causes of death following removal or destruction of the suprarenal cortex is acid intoxication, due to the accumulation and retention of the acid end products of normal metabolism. In the absence of the cortical hormone, the kidneys apparently fail to properly perform their acid eliminating function in relation to the neutrality regulation of the body. For some time following bilateral extirpation of the adrenals, the animal remains without symptoms, then mild symptoms, such as anorexia, lethargy and weakness, develop. The animal finally droops away into coma and dies with or without convulsions. The respiratory changes appear early. For some time, in some of the cases for five or six days, the respiratory mechanism is adequate to take care of the slowly devel-

oping acidosis by throwing off volatile acid and the pH remains within the normal range, *i.e.,* the acidosis is compensated. Finally, there comes a time when the respiration proves unequal to the task and the acidosis becomes uncompensated with falling pH and marked symptoms of acid intoxication. The respiratory mechanism soon breaks down and death ensues from respiratory failure. The change from compensated to uncompensated acidosis may occur with surprising rapidity. Bilaterally operated cats exhibiting only mild symptoms of acid intoxication may live for days in a lethargic, semi-stuporous condition with low alkali reserve, and suddenly pass from compensated to uncompensated acidosis with falling pH within a few hours, and die from respiratory failure.

Whether or not the suprarenal cortex plays any immediate and direct rôle in maintaining the normal acid-base equilibrium of the body is unknown. The probable view appears to be that the cortical hormone acts through the mediation of the kidney, by regulating and controlling certain of its acid eliminating functions. However, it should be stated that thorough histological study of the kidney of epinephrectomized animals has failed to reveal noteworthy pathological changes. But it should not be forgotten that once the animal exhibits symptoms of adrenal insufficiency it rarely survives more than five or six days at the most and generally a shorter period—*e.g.,* cats.

It is interesting to note that the acid intoxication of adrenal insufficiency is similar to that characteristic of the terminal stages of certain types of nephritis. The usual state of the acid-base balance that has been observed in nephritis is that of compensated alkali deficit (lowered blood bicarbonate with normal pH) which finally develops during the premortal coma into uncompensated alkali deficit with very low bicarbonate and falling pH. In both types abnormal acid formation, such as characterizes diabetic acidosis, is wanting. In adrenal insufficiency and nephritis with acidosis, there is phos-

phorus retention and rise in unknown organic acids. This raises the question whether or not failure of cortical function has any bearing on the problem of nephritis. Is it possible that breakdown or injury to the suprarenal leads to pathological changes in kidney function, and that certain types of nephritis characterized by nitrogen retention and acidosis have their real origin in lesions of the cortex? It is interesting to speculate on this possibility, especially since it is definitely known that the suprarenal cortex of individuals dying in the uremia of terminal hemorrhagic Bright's disease are hypertrophied. Moreover, it has recently been reported (MacKay and MacKay, 1926) that the suprarenal cortex of rats dying from experimental uremia likewise show hypertrophy. Certain changes in the blood of bilaterally operated cats are of interest in this connection. The inorganic phosphorus, non-protein nitrogen and urea are markedly increased in the blood of animals showing severe symptoms. The phosphorus and nitrogen retention indicate defective kidney functioning. However, fact and speculation should not be confused, since the relation, if such exists, between adrenal cortex and nephritic lesions awaits demonstration.

In recent papers, Rogoff and Stewart (1926) lay considerable stress upon the marked congestion and hemorrhage almost invariably present in the gastrointestinal tract of dogs dying from suprarenal insufficiency, as a contributory cause of adrenal death. They state: "It will suffice to point out here that in a very considerable number of the cases, the condition of the gastrointestinal mucosa is of itself assuredly incompatible with health and sufficient to account for the quickly fatal result." However the case may be with dogs, congestion and hemorrhage of the gastrointestinal mucosa plays no important rôle in the syndrome following bilateral epinephrectomy in cats. Autopsy of numerous individuals dying from adrenal insufficiency (respiratory failure induced by acid intoxication) have failed to show either

hemorrhage or very marked congestion. Many of our animals have survived as long as eight, ten, or even twelve days (treated by forcing fluids). Other untreated cats have survived five days (see protocols). Bloody stools have rarely been encountered, and are not significant since unoperated cats occasionally have some blood in the feces. Bloody urine was seen once. Fifteen of our animals have been autopsied within three to five minutes following death, but the gastrointestinal tract presented nothing unusual.

Cats also differ from dogs in one other respect in regard to their reaction to adrenal insufficiency. Rogoff and Stewart state that vomiting is a common symptom. This rarely, if ever, occurs in untreated bilaterally operated cats. The only vomiting we have seen was induced by passage of the stomach tube when fluids were being forced.

It is evident that certain of the minor symptoms of adrenal insufficiency exhibited by mammalian species may not exactly be the same as those common to other species. At any rate the gastrointestinal changes observed in epinephrectomized dogs is a secondary result and not a primary cause of death. In fact, the writer does not attach any significance to such changes simply because they are absent in cats.

Most observers have noted lowering of the blood sugar following the onset of serious symptoms of adrenal insufficiency, and the hypoglycemia of advanced Addison's disease has long been known. However, much of the older literature dealing with adrenal extirpation can be safely ruled out on the ground of poor operative technique. There can be little doubt of Stewart and Rogoff's contention that poor technique and operative shock are largely responsible for many of the results described by most of the early and also many later investigators of adrenal functions. Take, for example, blood sugar determinations: It is manifestly useless to determine the blood sugar of animals showing marked symptoms within

twenty-four hours following operation, because with good operative technique such symptoms do not occur.

In recent publications, Rogoff and Stewart state that the blood sugar is little, if at all, affected until near the end, when it may be moderately diminished and even then not constantly. Their work was done on dogs and carefully controlled. Our work on cats, however, shows that a gradual lowering of the blood sugar occurs coincident with the development of symptoms of lethargy and giddiness; and the fall is greatly accelerated as the animal passes into coma. As a terminal phenomenon the blood sugar may be as low as forty to fifty mgm per one hundred cc of blood, although slightly higher figures are more common.

The hypoglycemia, although severe in the terminal stages, is not the cause of death in cats because it can be corrected by glucose injections and yet the animal dies with typical symptoms. The writer believes that the moderate fall in blood sugar which does occur may be partly responsible for some of the early symptoms. In a recent paper this point was stressed, perhaps overstressed, because certainly more work needs to be done. It should be pointed out that all our low figures for blood sugar were obtained from animals either prostrate or in coma, and with but a few hours to live, and as stated previously, the blood sugar is very low as a terminal event. In the early stages of adrenal insufficiency, the blood sugar is generally around eighty or seventy-five mgm per one hundred cc. The normal blood sugar is variable and ranges from 100 to 115 mgm. The protocols listed in this paper give some data regarding blood sugar after bilateral epinephrectomy.

Even if hypoglycemia be conceded to be a symptom of adrenal insufficiency, it can not be due to loss of medullary tissue, but is due to absence of the cortex. This is indicated by the fact that bilaterally operated cats remain normal with normal blood sugar level so long as a piece of the cortex is left *in situ*, but when this is later

removed, the terminal blood sugar is as low as in those animals from which both adrenals were entirely removed.

The life-span of bilaterally epinephrectomized dogs and cats can be considerably lengthened by certain procedures, and is increased during certain physiological states of the organism.

Thus in 1913, H. A. Stewart published an account of his experiments on the effect of pregnancy on the survival period of double operated cats. His data clearly indicated that pregnant cats survive much longer than non-pregnant animals. His work has recently been extended and confirmed by G. N. Stewart and Rogoff (1925) working with dogs. They also find that pregnancy prolongs the survival period.

These same authors observed that intravenous injections of Ringer's solution and dextrose greatly prolongs life of epinephrectomized dogs. Zwemer (1925), working with cats, was able to keep his double operated animals alive for considerable periods by administering a 5 per cent. solution of glucose orally. Corey (1926), working in our laboratory, has demonstrated clearly that the survival period of bilaterally epinephrectomized cats can be greatly prolonged by forcing fluids. Almost any kind of fluid is efficacious, even water and milk, providing large quantities are given. Some of Corey's cats survived ten days. The fluid intake must begin a few hours following the second operation and be continued two and three times daily.

The explanation why forcing fluids prolong the life of double operated cats and dogs is not entirely clear. It seems to partially relieve the dehydration which is one of the train of symptoms of adrenal insufficiency (in cats at any rate), and possibly by the consequent diuresis, flushes toxic substances out of the organism. This explanation fits in with what we know about the acid intoxication of adrenal insufficiency. Why pregnancy and lactation should prolong life is not at all clear, any more than why first removing the thyroid gland of cats before

extirpating the adrenals tends to prolong life beyond the usual survival period (Zwemer, 1926).

The suprarenal cortex may and probably does have other functions besides the one stressed in this paper, but we, at present, know little about them. The next step in the problem is to obtain an extract from the suprarenal cortex which will relieve the acid intoxication of adrenal insufficiency. Such work is now in progress in this laboratory.

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THE IMPLICATIONS OF THE DIFFERENTIAL GROWTH RETARDATION IN CONDITIONS OF THYROID DEFICIENCY[1]

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THIS discussion is an extrapolation from the results obtained in the investigation of the rôle of the thyroid in growth and related data. It is purely and simply a synthesizing speculation.

When thyroid deficiency is produced in the albino rat 23, 30, 50, 65, 75 or 100 days of age, body and organ growth in weight is retarded. This reaction is not confined to the species but is general in all those animals which possess a thyroid gland so far investigated, not excepting the amphibia *after* metamorphosis. That the reaction should be non-specific is evident from the principle that "the rôle of the thyroid in growth is that of a participant in the regulation of the metabolic level through which is determined the rate of the maintenance processes of the organism and hence the amount of material presented to the cells for growth purposes during a given period" (26).

The query naturally arises as to whether this growth retardation in a given species is proportionate or disproportionate. That is to say, whether in the animal which is smaller than that to be expected for the age, the size interrelationships of the organs and the relation of organ to body size is the same or different from that of either an animal of the same age or of a younger animal of the same body weight.

A study of the data obtained in my series shows definitely that the end-result is an animal in which the inter-organ weight relations and the organ-body weight relations are neither those found in normal animals of the same age nor in younger normal animals of the same body weight. This is because the several organs differ

[1] Studies of the Thyroid Apparatus. XLVI. Read as part of a symposium before a joint session of the sections of medicine and chemistry of the American Association for the Advancement of Science, Philadelphia, December, 1926.

among themselves with respect to the degree of growth retardation they experience under these conditions. Hence it is clear that the growth retardation has been disproportionate and that modification of bodily structural relations has been produced. These facts are easily ascertainable from the preceding papers of this series.

Now the direction of deviation of inter-organ relationship is in general the same, regardless of the age at which the thyroid deficiency is initiated. This being so indicates that the particular type of disturbance here induced tends to produce a particular type of reaction out of which is evolved a modified type of organism of particular structural relations. That is to say, the modification is rather consistently in a definite direction. While this is obviously what should occur, in view of the essential relation of the organism to the metabolic function of the thyroid, its appearance in these data is evidence as to their basic reliability for general interpretative purposes.

A statistical study has brought out the fact that the variability of the thyroid in weight as measured by the coefficient of variability is greater than that of any other organ in the adult albino rat. It is also a fact, too well known to need direct citation, that the thyroid is exquisitely sensitive to dietary, temperature and seasonal changes, responding not only by perceptible alterations in size, but also in iodine content. These changes are indices of changes in functional activity. The warrant is clear that climatic difference may well be a factor in the production of difference in functional intensity of the thyroid.

The geological record shows that profound climatic and seasonal changes have swept over large areas of the earth's surface during past ages; that these changes were not catastrophic in character, but were gradual in their development and recession, and that they were spread over hundreds of thousands if not millions of years during which reproductive activity produced countless generations of animals. Paleontological studies indicate ebbings, flowings and migrations of flora and fauna, likewise spread over countless ages.

The shifts in climate which were consistent in one direction for long periods were indubitably factors in the shifts in flora and also in the bringing about of migrations of the fauna to new fields, thus inducing changes in dietary habits and materials.

It would seem as if these uni-directional shifts in environmental factors must indeed have induced alterations in the level of functional activity of the thyroid gland. While the type of change in the thyroid would be dependent on the type of climatic and dietary shift, it would nevertheless be consistently in one direction, according to the direction of the environmental factors, and continuous over long periods of time through countless generations.

On the basis of my experimental data it is just to conclude that situations such as described above would be reflected in the body as a whole and would be productive of a modification of inter-structural relations in a particular direction. The logical deduction is that thyroid function may well have been a significant factor in the production of varieties within a species if not of species within a genus, during the agelong course of evolution of those animal types which possess the gland.

A second extrapolation is indicated.

It can justly be assumed that a modification of the relative functional intensity of the several organs of the body is a natural consequence of the modification of their weight inter-relationships. This shift can also be considered as uni-directional, since the cause thereof is consistently of the same nature in all the groups. Hence there is obtained an animal in which the participation of any single organ in the totale of the metabolic processes is different from that normally found. The whole character of the metabolism is altered, as well as the rate, and altered in one direction.

Now the chromosomes, the probable carriers of hereditable characteristics, are complexes of chemically simple organic compounds. As such they are conceivably subject to chemical alteration by adequate change in chemical or metabolic environment. There is no chemical justifica-

tion for exempting the germ-cell chromosomes from this principle.

If chromosome chemical composition is affectable by adequate agencies, to the end that a shift in its nature is produced, then it can be expected that an alteration of offspring character can be produced. And if it is affectable the potentially adequate agency would be a fundamental shift in the character of the metabolic milieu, since the chromosomes are at one and the same time the products of and the contributors to the general type specific metabolic environment. Note that I write the character, not the degree, for a shift in degree would largely affect the speed of and not necessarily the type of reaction.

Since such a metabolic shift occurs in conditions of thyroid deficiency, it is possible that the sensitivity of the thyroid gland to changes in the external environment, which being repeatedly brought into play in one direction over long periods of time, might well provide a mechanism through which the inheritance of acquired characters is producible.

The obvious objection to these speculative conclusions is the fact that there are many species of living organisms which do not possess a thyroid gland, and hence what has been written here has only a limited, indeed no significance at all. Maybe so.

The crux of the interpretation in its general applicability is not centered on the thyroid as such, but on the thyroid as a factor concerned in the maintenance of the metabolic milieu characteristic of the species possessing the gland; and that, thyroid or no thyroid, a fundamental distortion of the character of the metabolism (*i.e.*, of its inter-constituential relations) is potentially an adequate mechanism whereby varieties within a species, species within a genus and the inheritance of acquired characters are possibly producible.

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SYMPOSIUM ON SOME BIOLOGICAL ASPECTS OF MEDICAL PROBLEMS[1]

MYCOLOGY IN RELATION TO HUMAN PATHOLOGY

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IN view of the increasing number of fungi which are being isolated from lesions or are found associated with other pathological conditions of man and other animals, and described as new genera and species of pathogens, it would seem to be to the mutual advantage of mycologists and plant pathologists as well as human pathologists to have a better understanding of each other's problems and to cooperate in their investigation and solution. With this aim in view, I have undertaken to discuss briefly some of the problems which should be of mutual interest and which are deserving of far greater attention than they now receive.

Mycology deals with that part of the vegetable kingdom commonly called "fungi." There are a hundred thousand or more specific names of fungi in mycological literature. These organisms are so diverse in size, shape, biological character and relationship that it is obviously beyond the power of any single individual to know them all. They include all manner of forms and conditions from obligate parasites to general saprophytes. Polymorphism, pleomorphism and heterothallism prevail.

This vast group of plants falls chiefly in three large natural divisions, Phycomycetes, Ascomycetes and Basidiomycetes. The Phycomycetes are the lowest and the

[1] Symposium before a joint session of the sections of medicine and chemistry of the American Association for the Advancement of Science, Philadelphia, December, 1926.

bacteria are sometimes included among them. Most of this group consists of simple or branched filamentous forms usually producing sporangia with conidia or zoospores and oospores or zygospores which arise from the union of two gametes. The common black mold, Mucor, is probably the most familiar member of this group. The Ascomycetes include a very great variety of forms ranging from the simple yeasts to the large, fleshy, edible morels. All are characterized by the production in their final fruiting stage of ascospores, mostly eight in number, borne in more or less elongated small sacs called asci. The third group, the Basidiomycetes, is also very diverse in form and size, varying from filamentous forms to the huge puff-balls and toadstools. The spores in this group are usually produced in groups of four at the top of a more or less club-shaped or oblong swollen cell called the basidium.

There is another great group of asexual forms producing conidia and pycnidia generally treated under the head of "Fungi Imperfecti," or more recently called Deuteromycetes. Most of these are believed to be stages in the life cycles of ascomycetous fungi. In many cases the genetic relation of such forms has already been demonstrated by pure cultures from single ascospores. In this way it has been shown, for instance, that conidial forms which have been referred to the so-called genus Monilia on account of their similarity in morphological characters are stages in the life cycles of widely different genera of Ascomycetes. For example, *Monilia cinerea* is the conidial form of *Sclerotinia cinerea,* a Discomycete causing brown rot of fruit. *Monilia sitophila* is the conidial form of a Pyrenomycete closely related to Melanospora which is a frequent pest in bakeries. What the perfect stages of the other numerous species which have been referred to Monilia may be remains, in most cases, to be determined.

These conidial forms are able in many cases at least to propagate themselves more or less indefinitely without

the production of the ascospore stage. Some conidial forms are thought to have lost their perfect stage or have become permanently separated from it, so that they now behave as autonomous organisms. Complete proof of this, however, is difficult if not impossible to obtain. Until every known Ascomycete has been connected with its conidial stage or stages, leaving a residue of conidial forms without perfect stages to connect them with, can we assume autonomy for them, and even then there is still the possibility that the perfect stage is among the species yet undiscovered or undescribed. In most cases ascospores must be used to start cultures in order to determine the life cycle, as most conidial forms which are known to have ascogenous fructifications do not usually produce them in artificial cultures made from conidia. This is probably due in most cases to our failure to provide the proper culture media and conditions for the full development of the organism.

Another complication is sometimes the cause of failure to obtain the perfect form of fructification of the fungus. It has recently been discovered that some Ascomycetes are heterothallic, *i.e.,* they consist of individuals of opposite sex both of which must be present in a culture in order to obtain ascogenous sporocarps. Either sex will produce an abundance of conidia when grown alone but no ascospores. This important fact must be taken into consideration in all future work on the life histories of the Ascomycetes.

Of the hundred or more species of fungi which have been found associated with or causing pathogenic conditions in man, most belong to the great group of imperfectly known conidial or mycelial forms. There are two rather distinct problems involved in the study of this group of organisms. One concerns the origin, identity and life history of the organism; the other its pathogenic or other relation to the lesion or other pathological condition with which it is associated. The exact relation of any specific fungus to the pathological condition involved is frequently obscure or uncertain.

The old idea of a more or less definite division of fungi into two groups, parasites and saprophytes, has been abandoned, as it is now known that all sorts of intermediate forms exist which are included in a large and rapidly increasing group, known as facultative parasites. They develop in the host and cause injury only when introduced into lesions or when the host is in an abnormal or weakened condition. From all that is known of the life history and relationships of the fungi met with in man it appears that but few are obligate parasites. Most of them would be classed as weak or facultative parasites. The determination of the exact causal relation of the organism to the pathological condition with which it is found is a pathological problem which can only be solved by thorough study and inoculation experiments with pure cultures of the organism. The problem on which the properly trained and equipped mycologist might be able to render assistance is that connected with the determination of the origin, identity, life history and relationships of the fungi concerned.

A knowledge of the natural habitat and various modes of reproduction and dissemination of the near relatives of the pathogens may furnish valuable clews to the origin and history of the organisms and the sources and conditions of infection and thus help in the discovery of successful methods of prevention or cure.

It should also be remembered that many of the microfungi are of such a mutable or plastic nature in their vegetative or hyphal condition as well as in their physiological or pathological peculiarities that comparatively slight differences in host, culture medium or environment may produce remarkable changes in their growth and appearance. In one case an organism may produce a considerable growth of hyphae or mycelium and in another the same organism may give only a scanty growth of quite different appearance. In some cases the growth may be aerial and in others immersed. There is so much variability in the amount, character and appearance of

the vegetative hyphae in many of the micro-fungi, especially those to which most of the human pathogens have been referred, that their positive identification under cultural conditions is extremely difficult. Some method must therefore be devised to produce normal sporulation and development of the fungi in order to determine their true identity and relationship. This is primarily a mycological problem.

Most of the species of pathogenic fungi already named and described in medical literature need to be more carefully studied from a mycological standpoint and compared with related non-pathogenic organisms in order to determine their synonymy and taxonomic status. Such common fungus names as Monilia, Oidium and Sporotrichum are frequently applied to quite different fungi by the mycologist and the pathologist. An excellent illustration of this is to be found in the case of the thrush fungus, widely known and studied for nearly one hundred years. It has had a variety of generic and specific names, as *Oidium albicans, Sporotrichum affinis,* Monilia, Dematium, Endomyces, etc., and there is still no general agreement as to its exact identity and relationship. If further examples of this are desired, Achorion, Trichophyton or Microsporon with their various synonyms, species, varieties and forms might be cited.

One of the chief difficulties in this connection is probably the same that is met with in plant pathology, and that is the existence of many species which include several morphological varieties and physiologic forms, showing different pathogenic characters. These latter the plant pathologists have agreed, for the sake of uniformity and convenience, to designate by number instead of by separate name. The multiplication of names for all sorts of poorly defined varieties, forms and conditions of fungi leads to misunderstanding and confusion rather than to the advancement of knowledge.

Closer cooperation of mycologists and pathologists should lead to greater uniformity in the categories recog-

nized and in the terminology and nomenclature employed for these fungi. Many of the true fungi encountered by medical men, especially the organisms found in the respiratory and digestive tracts, belong to common and widespread groups, such as Penicillium, Aspergillus, Mucor, Oospora and Trichothecium. Most of the species of these genera are more or less ubiquitous and not usually parasitic. They sporulate readily in artificial cultures and can generally be identified with a reasonable degree of certainty.

Other organisms, however, such as those referred to Trichophyton, Acorion, Microsporon, etc., generally referred in medical works, to the so-called Dermatomycetes are much more difficult to determine on account of their unsatisfactory development and failure to sporulate normally in culture. Some of the bodies which have been described and figured as asci or spores in connection with these fungi are of very doubtful validity and are in need of much further study.

Usually the more parasitic an organism, the more difficult it is to induce it to grow and produce spores in artificial cultures. In the case of the obligate parasites, one should expect to find special forms or modes of reproduction and dissemination adapted to a strict parasitic habit. According to recent investigations, the organisms referred to the Dermatomycetes appear closely related to the small ascomycetous fungi belonging to the Gymnoascaceae. In a recent paper by Dr. Arturo Nannizzi, of Siena, Italy, entitled, "Ricerche sui rapporti morfologici et biologici tra Gymnoascacee e Dermatomiceti," published in "Annales Mycologici," Vol. XXIV, no. 1/2, pp. 85–129, 1926, is an excellent presentation of a comparative study of the so-called Dermatomycetes with the common Gymnoascaceae, which would seem to show a very close relation between some of the organisms found in the dermatomycoses of man and the saprophytic fungi belonging to such genera as Gymnoascus and Arachniotus.

A very good general discussion of the parasitic fungi of man, by H. C. Plaut, is to be found in Kolle and Wassermann's "Handbuch der Pathogenen Mikroorganismen," Volume 1, 1903. This work is probably familiar to all who use the German literature on this subject. Much of the best work is in foreign languages, such as Latin, French, German and Italian. A useful publication treating of some of these fungi from a mycological standpoint in English is W. H. Emig's "The Occurrence in Nature of Certain Yeast-like Fungi with Reference to their Possible Pathogenicity in the Higher Animals," published in Annals of the Missouri Botanical Garden 3: 243–307, April, 1916. This is a descriptive paper with a good general bibliography of the important literature. The paper by Nannizzi already referred to also contains an excellent bibliography, including most of the recent important works on the subject. An adequate summarization in English of the present knowledge of these organisms, which is now scattered through numerous publications in various languages, would be of the greatest value to English-speaking workers in this field of medical research and mycology. It would provide a convenient source of information as to the present status of our knowledge and furnish a better basis for future work on both the mycological and pathological problems.

It appears evident from even a superficial survey of this field that the mycological problems involved in the study of human parasites are so great that cooperation between the pathologist and the mycologist is desirable, if not essential, for their solution. The medical investigator could scarcely be expected to possess the training, experience and time necessary to solve them for himself. The services of the protozoologist, the helminthologist, the entomologist and the mycologist are becoming more and more important in the solution of many of the problems of human pathology in which parasites are involved.

For the mycological work in this field a background of exact knowledge of the lower groups of fungi, especially

Ascomycetes and their life histories and a general understanding of the fundamental problems of plant and animal pathology, is necessary in order to successfully overcome the difficulties involved in determining the identity, relationship and pathogenicity of the fungi encountered. There are hundreds of so-called species of these groups, poorly described and little known. The extent of the subject and the difficulties involved make it necessary to devote the entire time of well-trained specialists to it in order to make any important contributions to our knowledge. Training in bacteriology is generally recognized as essential for the investigator in human pathology, as bacteria are much more numerous and important in medical work than the true fungi. The successful study of the filamentous fungi, however, requires special knowledge of the pathogens, as well as of technique and media not ordinarily possessed by the medical bacteriologist. On the other hand the mycologist lacks the medical training and point of view necessary in attacking the pathological aspects of the problem.

An important aid in the study of these problems is the maintenance of pure culture supply laboratories prepared to furnish correctly named cultures of the fungi with which the medical mycologist and pathologist have to deal. Such a laboratory has already been established in connection with the McCormick Institute at Chicago and should be actively supported and encouraged by all who are interested in the advancement of our knowledge of this subject. Every effort should be made to make this collection as complete as possible.

The most important step, however, which needs to be taken in order to meet the needs of the present situation as we see it, and to promote the best interests and advancement of both mycology and this field of human pathology, is to secure the services of a thoroughly trained and experienced mycologist, especially familiar with the lower Ascomycetes, their life histories and culture requirements, as a permanent member of the staff

of each large medical research institution and provide him with the necessary assistants and equipment to make thorough and detailed studies of this group of organisms, in cooperation with the pathological investigators. This, we believe, is the most feasible and promising method of reaching a solution of some of the vexing problems connected with this subject.

This field at present does not promise such thrilling and epoch-making discoveries as have rewarded research in medical protozoology and entomology, but still we believe it can claim enough human and medical importance to justify the action suggested.

HUMAN TYPES IN RELATION TO MEDICINE[1]

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HUMAN types have been of interest to men of medicine at least since the time of the Greeks. The four humors of the Hippocratic School (1), yellow bile, phlegm, black bile and blood, were related to the four elements of Aristotle (20), fire, water, earth and air, respectively.

The humor choler, or yellow bile, or fire, was described as hot and dry, begotten of the hotter parts of the chyle and gathered to the gall. It was supposed to help the natural head and senses.

The humor phlegmatic, or phlegm or water, was described as cold and moist, begotten of the colder parts of the chyle in the liver. His office is to moisten the members of the body.

The humor melancholy, black bile or earth, was described as cold and dry, thick, black and sour, begotten of the more feculent part of the nourishment and purged from the spleen. It is a bridle of the two hot humors, blood and choler, preserving them in the blood and nourishing the bones.

The humor sanguine, blood or air, was described as a hot, sweet-tempered, red humor, prepared in the meseraic veins, and made of the most translucent part of the bile in the liver, whose office is to nourish the whole body, to give it strength and color, being dispensed through every part of it, and from it spirits (air) are first begotten in the heart, which afterwards in the arteries are communicated to other parts.

Aristotle (20) studied and taught physiognomy, which in original Greek means interpreter of nature, and the physicians Hippocrates and Galen (1) believed that the

[1] Symposium before a joint session of the sections of medicine and chemistry of the American Association for the Advancement of Science, Philadelphia, December, 1926.

different kinds of moisture in man's body, as they predominate, determine the temper and disposition of the mind. An exact balance of the four humors makes a sound and well-constituted man and provides for the undisturbed processes of digestion and assimilation.

The School of Salerno (14) taught the four temperaments, elaborated their dispositions and described their common ailments. This school had many celebrated physicians and patients, especially during the Crusades.

The choleric temperament was described as hot and dry like fire, of dark red complexion, jovial, quick and jolly, conceited and ambitious, aspiring to great fortunes, proud, bountiful, but malicious, spiteful and hard-hearted; bold as a speaker and bolder as a liar, easily provoked to great anger; eating a great deal, but ever looking thin and pinched; precocious, and late in life hairy. When ill they seem to have been affected particularly with ringing of the ears, insomnia and constipation, with vomiting, great thirst, slimy stools, bad stomach and poor appetite. The heart beat was rapid and the pulse hard, the temperature abnormally high, with sour spittle and fiery dreams. Indigestion is paramount.

The phlegmatic temperament was described as heavy and dull of sense, cold and moist like water, although fair and white in complexion, short and fat and square, fond of ease, rest and sloth, content with scant knowledge and with great dread of pain. Their spirits dead, their senses dull, they sit and spit to avoid the phlegm. Yet with all these qualities the phlegmatic are fair. Their illness usually takes the form of intense salivation, pains down to the waist, slow digestion, head and stomach aching; with empty veins and soft slow pulse and placid dreams. This seems to point to a plethoric condition with a bad heart.

The melancholic temperament was described as like cold, dry earth, swarthy and "colly," exceeding studious, ever solitary, refusing sport and ease and company, pensive and musing; storing up revenge and secret hate;

constant in choice but slow in choosing, extreme in love but seldom lustful, suspicious and mistrustful; sly wit, thrifty, heavy in appearance and not a dare-devil. The maladies are apt to drive them mad, a weak, fantastic brain, false joys or perpetually sad, with dreams like visions and ill apparitions; the pulse and heart beat hard, the water thin, the color dark and bad, and the stomach bitter, with the left ear ever burning. The kidneys apparently give the most trouble.

The sanguine temperament was described as warm and soft like air, like roses and bright lilies in complexion, jovial, quick and jolly; gamesome, and loves wine, women and all recreation; is fit for all company and every fashion, likes pleasant tales, news, plays, cards and dice; bold, but not apt to take offense, not ireful, but bountiful, kind and cheerful; inclining to obesity and prone to laughter, loves mirth and music, cares not what comes after. Their illness takes the form of red and fat exterior, staring eyes, short, soft pulse, full veins, large belly, restless sleep and sexual dreams, forehead of grief, sweet, abundant saliva that irritates the mouth.

The four temperaments—choleric, phlegmatic, melancholic, and sanguine—have been related to the four diatheses—phthisical, plethoric, catarrhal and rheumatic, respectively. They have been depicted in art by Albrecht Dürer in "The Four Apostles." A pseudo philosophic psychology elaborated them and they have been taught in certain schools as standards for the elucidation of character and conduct. This approached palmistry, physiognomy and phrenology and has been dropped.

A more recent description of four types in Europe has been developed in France and Germany. Chaillou (7) and MacAuliffe (8) were the first to present the types in great detail with drawings and photographs, although they were first described by Sigaud (24), and concurrently by Tricolet (29). The types are called cerebral, respiratory, digestive and muscular. They do not make up the entire population, hardly half of it, about 40 per

cent., not counting the mixed and mosaic forms and others that can not be classified. The types may be seen in any hospital population, however, and they will be described as given by Chaillou and MacAuliffe.

In the muscular type the face is rectangular, vertical in front, no prognathism, and the distance from the top of the forehead to the glabella, from the glabella to the nasal spine, and from the latter to the chin are equal. These three parts of the face differ in the other types. The upper part is large in the cerebral type, the middle part in the respiratory, and the lower part in the digestive. The nose in the muscular type is straight or sinuous, high and somewhat rectangular. The neck is broad, well filled with muscle, but not necessarily short. The shoulders are horizontal as are the clavicles and acromion processes. The iliac crests are not very wide, but the costal angle is about 80°. The profile of the trunk is convex in front and straight behind. The extremities are usually long, and the muscles are strongly developed. There are several sub-types of the muscular, a long and a short, a musculo-cerebral, a musculo-respiratory and a musculo-digestive. The type with its variables makes up about 40 per cent. of the population in France.

The cerebral type appears in about 14 per cent. of the population, is the rarest of all the types and represents the product of civilization. It occurs more often in late Egypt than in early Egypt. It is increasing in those places where civilization is advancing. The type is characterized by a small and slender body, a large and rounded head, remarkably developed upper face and reduced lower face. The frontal and parietal bosses of the head are well developed, the side view is spheroidal, with a high auriculo-bregmatic diameter. The index is hyperbrachycephalic. The trunk is slender, the extremities short, the hands and feet small. There are mixed types as for the muscular.

The respiratory type occurs in about 30 per cent. of the people. The middle part of the face is extremely

well developed, the nose long, the maxillary bone large, the zygomatic bones prominent, all the accessory sinuses of the nose including the mastoid are large. The eyes are far apart because of the large size of the nasal cavity, and the orbits are well separated. There is superior prognathism because of the large size of the maxillary bones. The face is lozenge-shaped because of its large size in the middle. The cranium is mesocephalic more than in the muscular type. The neck is long and well filled, especially about the larynx, which is large, with a prominent Adam's apple. The thorax is large and long, and the abdomen reduced by the size of the thorax, which reaches nearly to the iliac crests. All the muscles of respiration are well developed, but those of the extremities are not. The persons are usually thin. The joints are not rough and prominent as in the muscular type, nor are they small and graceful as in the digestive type. In the female they are specimens of grace and beauty, tall, delicately molded, with an oval face; they represent the Raphael and Leonardo da Vinci types. The respiratory-cerebral types are common, but the respiratory-digestive are rare and the respiratory muscular not uncommon.

The digestive type is not common, although present in about 20 per cent. of the people. The outstanding characteristics are the large lower face, huge jaws and extremely ponderous abdomen. The mandible and zygoma are unusually well developed, and the teeth are large, regular and well formed. As age advances the double or triple chin becomes evident, fat accumulates about the buccinator muscles, the masticators and the parotid gland about the ear, and this part of the face seems monstrous, and even raises the lobule of the ear and extends it forward. In spite of appearances the trunk is small. Its form is that of a cylinder slightly flattened in front and behind. A pad of fat covers it. The size of the abdomen reduces the size of the thorax considerably, making it short. The extremities are very long, the shoulders broad, the reach much greater than the stature. Mixed

types are common, and the digestive-muscular type is a veritable giant in some cases.

The wrestler type of Bauer (3) is a mixed digestive-muscular type, built like an inverted pyramid with a ball, the head, on top of the base. The shoulders are exceptionally broad, as is the thorax. The type is tall and heavy, and the muscles of the chest, arms, shoulders and neck are unusually well developed. The digestive type has also wide shoulders, but compared with the wrestler the difference is great. Bach (2) found three sport types after studying 85 indices, measurements and percentage relations of each person among 3,457 German athletes, 710 students, 95 amateur wrestlers, 33 professional wrestlers and 33 men of the digestive type. The types are called tumbler or gymnast, pentathlon and wrestler. The gymnast has a relatively long trunk, with a great development of breadth in the shoulder girdle. The pentathlon has long legs and relatively small dimensions in breadth. The wrestler has been described above.

Kretschmer (19) gives three types in psychiatric material, asthenic, muscular and digestive, and Henckel (15) finds the same types in Sweden and Bavaria in similar material, with the conclusion that all three types are to be found throughout Europe among the great races. One interesting feature of the investigation by Henckel is that the digestive type showed only 4.9 per cent. of incidence for dementia precox among the Swedes and 2.0 per cent. among the Bavarians, whereas the type showed 63.4 per cent. of incidence for maniac-depressive insanity among the Swedes and 57.6 per cent. among the Bavarians. The digestive type is thus shown to have a predisposition for maniac-depressive insanity, and a tendency not to have dementia precox. Ritterhaus (23) shows that only 3.7 per cent. of Nordics have general paresis, whereas 20 per cent. of eastern Europeans and 40 per cent. of central Europeans have this disease. He gives as the reason that the Nordics have not the powerful and grossly sensual sexuality of the other peoples.

The relation of these types to disease has yet to be investigated in detail. The pure types are found in small numbers, the mixed types in greater numbers and a small percentage of the population can not be assigned to any of the types. Bauer found among 2,000 patients that 43.3 per cent. were pure types, and 56.7 per cent. were mixed, although 8.5 per cent. were of doubtful type.

Other types have been found, such as the apoplectic, phthisic and asthenic of Stiller (25), the megalosplanchnic (apoplectic), and mikrosplanchnic (phthisic) of Viola (30), the fifteen sport types of Kohlrausch (17), the sport types of Thooris (27) similar to the muscular and digestive, and even the five or six types of athletes in the Olympic games in the time of Philostratus Flavius.

Draper (10) has studied man in relation to disease by measuring each person ill of a certain disease, and in this manner has established what he calls a gall bladder type, a gastric ulcer type, and so on.

After a careful survey of all these types I am more convinced than ever that a simpler designation is better, and prefer the two types as first demonstrated by Manouvrier (21) and Godin (12). Manouvrier found that by taking 10 per cent. of the extremes in breadth and length of measurable parts of the body two types resulted that he called Brachyskéle and Macroskéle, or broad skeleton and narrow skeleton. Godin applied this to growing children and showed that the greatest difference between the two types is in the relation of leg length to sitting height, or sitting height index. We thus have two types, one broad, stockily built, with long torso, large hands and feet, short extremities and drooping shoulders; the other slender, with narrow parts, short torso, long extremities, small hands and feet, and square, straight or elevated shoulders.

These two types were differentiated by the author from studies of the external anatomy, as well as anthropometric measurements, and the illustrations and de-

scriptions of the types have been published. A third type was added after studies of the Filipinos, Japanese and Chinese at first hand, and studies of other peoples from illustrations and the works of others. The first two types are the Hypermorph and Mesomorph, or high and middle form, and the third type is the Hypomorph or low form. The first two types are found in their most extreme form among the Whites, the last type only among the Blacks and Yellow-Browns (11).

The nose and ear have been used more than any other characters in the differentiation of the types. Therefore they will be described in some detail.

The Nose

The hypermorph nose is long, high and narrow, with high root, bridge and tip; the nostrils flare but little and open almost directly downward or slightly backward. The nose appears prominent and may seem to project from the face and be larger than it really is because the glabella and brows do not usually project as much as in the mesomorph. The nose may be aquiline, straight, sinuous or retroussé. Changes in the contours of the jaws and forehead may account for the difference between the aquiline and retroussé, although the first is an overdeveloped form and the last is underdeveloped.

The mesomorph nose is rather large, relatively broad, not very high, with apparently depressed root as a result of an angle instead of a curve between the nasal and frontal bones. It has a straight or slightly upcurved bridge or ridge, the tip may be long and turned somewhat upward, and the nostrils open downward or slightly forward. The lines alongside of the nose slope away from the median corners of the eyes to the lateral borders of the nostrils, which do not usually flare. The ridge of the nose and the lower border from the lip to the tip are usually straight. This gives a pyramidal appearance, a solidity, and a large-sized appearance to the nose, although it may not be very high or very long.

The hypomorph nose is broad and short, with broad depressed root and bridge, and the nostrils open rather forward than downward. The nostrils flare and are open wide, and the extremity of the nose is uptilted so that an instrument may be inserted horizontally along the floor of the nose without interference by the alae. The ridge of the nose is depressed or flattened, because the nasal bones do not form a steep roof over the nasal passages by their apposition along the midline. The articulation of the nasal bones with the frontal bone is a gentle curve rather than an angle. The supraorbital ridges are not prominent, nor is the glabella, and the frontal sinuses are small, but the cheeks are full and the eyes are prominent; therefore the front of the face is somewhat flattened, although the lips are thick and project forward. The type is semi-infantile and seems to be the result of incomplete development or immaturity.

THE EAR

The hypermorph ear is usually thin, long and narrow, delicately molded, and the lines of the skin are fine and close together. The helix often presents in extreme cases a thin, straight or slightly curved edge and is very slightly or not at all rolled over except at the top. The distance between the helix and anthelix is slight and the lower border frequently merges into the cheek without a lobule. The concha is long and narrow in conformity with the remainder of the ear. The anthelix is prominent and often projects beyond the helix, which is turned somewhat backward. The tragus and antitragus also project from the head beyond the helix and may be more prominent than either the helix or lobule. In extreme cases when looked at from either the back or the side the helix along its border may have a shape that resembles the italic letter *f* or the old English letter s. It is close to the head at the lobule and at the upper outer or lateral border, and it is farther away at the top and behind the concha. Neither the Satyr tubercle nor Darwin's tuber-

cle are prominent when present, or very large, in the hypermorph ear. It seems as if the helix had stopped growing early, but the other parts of the ear had continued to grow, resulting in a slightly contracted helix. The helix has failed to undergo retrograde metamorphosis by rolling outward and turning toward the concha as in the mesomorph ear and as found in its extreme form in the hypomorph ear, and it is therefore turned toward the head by the growth of the other parts of the ear.

The mesomorph ear is thick, large and heavy looking, rounded or quadrilateral, relatively short and broad, and sometimes flattened. The helix is well marked by a rather heavily rolled over edge, except at the lower border where the lobule is large and shelf-like or dependent. The concha is shallow and large, relatively broad and not very long. The tragus and antitragus do not project out from the head beyond the helix as in the hypermorph ear, nor do they stick down into the concha as in the hypomorph ear. The helix may be almost quadrangular in shape and flat, but when the person is fat the helix may stand out from the head above and below. The lines of the skin are large and far apart.

The hypomorph ear is usually small and round, thick and coarse with the edges of the helix rolled over almost into the concha to form a shelf-like upper ear and lobule. This sometimes resembles a similar condition in the mesomorph. The concha is broad, not long and deep, and the ear appears like a small bowl with a thick rim around all but one side. The tragus and antitragus do not stand out as in the hypermorph ear, but are depressed into the concha. The flaring ear must not be confused with the hypomorph ear, because the flaring ear is the result of a wide dorsal wall to the concha, and not to a thick helix which has rolled over and made a bowl-shaped concha.

There are a great many other differences between the three types; the internal organs are long, vertical and small in the hypermorph, broad, transverse and large in the hypomorph and similar to the latter in the meso-

morph. Stockard (26) calls the types lateral, or round, and linear, and gives other differences. The round has a tenor voice, the linear a bass voice; the round is anatomically near-sighted, the linear far-sighted; the round has low gonadal reaction, the linear high; the round has poor nerve control, the linear good nerve control; the round is good on details, but not so thoughtful; the linear more thoughtful but not so good on details; the round slow in differentiation or transformation in development, the linear faster; and the round has low thyroid metabolism, the linear high. The round may be said to be more judicious, the linear more executive.

Pure types are found in varying proportions in different parts of the world. Some populations are almost entirely of one type as the Negrillos and some Malays are pure Hypomorphs, but in Europe and America at present among white peoples there are the two types almost everywhere, and in different proportions. The bulk of the population is usually made up of mixtures of various kinds or those who are between the two extremes.

The author studied some three thousand patients and fifteen hundred postmortems in Manila, New Orleans and elsewhere, from which the conclusion arose that there seemed to be a tendency for the mesomorph to be susceptible to diseases of the tissues derived from the mesoderm, and for the hypermorph to be susceptible to diseases of the tissues derived from the ectoderm and endoderm. Such cases seemed to be abnormal for the type and were called mesodermapath and epitheliopath, respectively. A more extensive and intensive study in greater detail is needed before the exact relations of type and disease may be determined with accuracy.

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THE NEEDS OF MEDICAL ENTOMOLOGY[1]

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MEDICAL entomology, like so many other things, has just grown up. But it has grown more rapidly than most branches of knowledge, so rapidly, in fact, that many of us have watched it from its very beginning. And, like so many things that have "just grown up," it has developed without planning, and discovery has followed discovery, each one leading further in some one direction or opening up an entirely new line of promising investigation.

It is only six years since I wrote a "Sketch History of Medical Entomology" (so fascinating a task that it fairly wrote itself), and yet since that time many thousands of pages of reports of investigations in this direction have been published. Appreciation of the importance of such research has grown very rapidly indeed.

The medical entomologist is a new invention. Only a few years ago no medical man was an entomologist and no professional entomologist was a medical man. It is probably easier for a medical man to pick up a little entomological knowledge than it is for an entomologist to acquire any degree of medical knowledge. It is true that all the great discoveries in medical entomology have been made by medical men, for the most part unaided; but it seems to me obvious that, once the discoveries are made, entomologists should be called in immediately, for plainly the control of the insect vector of a disease is a problem for the economic entomologist above all others.

When I was first invited to take part in to-day's program the secretary of the section, Dr. Goldforb, and I decided upon the title "The Problems of Medical Entomology," the idea in both of our minds being that I might

[1] Symposium before a joint session of the sections of medicine and chemistry of the American Association for the Advancement of Science, Philadelphia, December, 1926.

point out and perhaps discuss the more important of the individual research problems still untouched or still insufficiently explored. But I hesitate to attempt this—there are so many of them.

So instead of this plan I shall discuss briefly five general needs as follows: (1) More trained medical entomologists; (2) more opportunities for them to work; (3) the study of forms related to those already proved to carry disease; (4) the correlation of results; (5) a centralized foundation where items 2 and 4 can be provided for and where a general scheme can be elaborated for a systematic covering of the whole field of possibilities and which should have enough funds to finance all investigations that bear on the subject.

(1) The most immediate need of medical entomology at present is to supply the medical entomologist. I have stated just now that he is a new invention. As a matter of fact he exists only theoretically, if we are to define him as a man who possesses an adequate knowledge of both pathology and entomology. *Ideally,* he should have such a combination of knowledge. *Practically,* one man—a pathologist—can work in the closest cooperation with another man—an entomologist. The two working together will the more quickly arrive at a just conclusion as to the identity of an insect vector than if the pathologist were to work unaided.

The identity of the vector once thoroughly established, the entomologist may devote himself wholly to the study of the biology and ecology of this insect in his effort to find some practical means of control.

Looking at it from this point of view, a medical entomologist may be defined as one who has expert knowledge of the insects that are known to carry disease and of insects closely related to them. To such a man a profound knowledge of pathology or of any other branch of medicine is unnecessary. A smattering will do; or he may even know nothing at all about it.

Let us say then that a medical entomologist is one who is thoroughly competent, through his previous training and previously acquired knowledge, to study the disease-bearing insects, and who is engaged in studying them. Such a man, theoretically, can not be one who has spent the formative years of his life in the study of medicine. He is worth far more in this direction if he has spent these years in studying insects. So that it is fair to say that medical entomology is primarily the study of insects that carry or may carry diseases—not the study of diseases that are carried by insects—and only secondarily the study of the way these diseases are carried by insects.

It has happened too often that medical men have thought that enough entomology can be acquired in a short time to enable them to speak and write learnedly on all aspects of disease communication by insects. Admitting that I may be looking at it in a one-sided way, it seems to me that this has been a more frequent error than the assumption of pathological competence by the entomologist.

Probably the medical men have felt a stronger incentive that induces them to carry their investigations to the farthest limit. But for the most perfect efficiency they should have associated with them men of sound training in entomology.

I was not particularly surprised to hear Dr. R. T. Leiper, a well-known helminthologist, at the International Entomological Congress held in Zurich late in June, 1925 (representing the feeling of the London School of Hygiene and Tropical Medicine), after dilating on the great importance of insects as vectors of disease, make a plea for a closer working connection between pure and applied entomology and emphasize purposely what he termed "a certain indifference among entomologists towards the needs of medical entomology." I resented this statement and combated it, and in this attitude I was very strongly supported by T. Bainbrigge Fletcher, of India, R. Stewart MacDougall, of Scotland, and C. B. Williams, of Egypt.

It is true that during the World War certain other nations called on their entomologists sooner than did the United States, but then they were engaged in the war three years before we were, and naturally appreciated the importance of these men at an earlier date.

There is no indifference on the part of entomologists; they are anxious to help. There are growing up among them men who are trained for this work. Not only are there certain great medical schools, notably perhaps Harvard and Johns Hopkins, that are giving training in medical entomology, but, aside from their medical colleges, other universities, like Cornell and Minnesota, are educating medical entomologists in the sense that the emphasis is upon *entomologists.*

I feel rather insistent upon the point that it is not necessary for an extremely efficient medical entomologist to possess a degree in medicine; and this has recently been brought home to me by the conditions existing in the great Liverpool School of Tropical Medicine and the London School of Hygiene and Tropical Medicine.

At Liverpool the learned and efficient entomologist, Robert Newstead, who has no college degree whatever (although a member of the Royal Society) and who was appointed originally on the nomination of Sir Patrick Manson, Sir Ronald Ross and Sir Rupert Boyce, reached the retirement age recently, and the appointment of his successor is delayed by the requirement by the governing board that the candidate shall possess an M.D. Several good men who have done excellent research work have been turned down on this account.

At the London School a similar requirement holds, but here, as Dr. Andrew Balfour told me the other day, they were able to find in P. A. Buxton a good entomologist who at some time in his life had accumulated a doctorate in medicine.

(2) The second need is to find more opportunities for these men to work. It is true that a competent man will make his own opportunity. He will work and achieve

results wherever he is. But he should receive every possible encouragement. He should receive adequate financial support and be permitted to spend his whole time on the many promising problems. As there are many such problems there should be many such men, and, given the proper support, there would be many such men.

(3) It is undoubtedly true that there is very much that is still unknown about the especial insects that have been proved to carry disease. The urge to find out about things—to solve the unsolved problems—is obvious. But there is another thing which is probably not quite so obvious. That is the need to find out everything possible about the insects that are most closely allied to the forms that have already been convicted and that may possibly be discovered to have disease-carrying possibilities. There are whole groups of these insects whose intimate biology is but little understood. These groups should be attacked from every point of view by a corps of well-trained workers.

Many of us remember how Ross's discovery was delayed for some time by the lack of knowledge of the different genera of mosquitoes and of the differing biology of these genera; and we remember also how scanty was mosquito knowledge when the news of his discovery was first flashed to the world. We remember how Giles went hurriedly to work and published the first edition of his book on mosquitoes, and how Theobald, with the aid of the British Museum of Natural History, in an incredibly short time wrote and published the first four volumes of his "Monograph of the Culicidae of the World." It was a fortunate chance that mosquitoes had already engaged the attention of the entomologists at Washington and that a bulletin was published in 1898 which not only plainly differentiated the principal genera of mosquitoes and gave rather full accounts of the biology of Anopheles and one species of Culex but went rather extensively into the subject of mosquito control; so that army sanitarians were able to use proved methods when they began their

clean-up of Havana and their subsequent admirable work in the Canal Zone.

How much time would have been saved had mosquitoes been adequately studied before Ross's discovery was made! At that time it was impossible to anticipate this discovery, but now many important fields are open.

Not only must we know everything possible about the life histories of all insects that bite the human species and domestic animals, or especially those species or groups of species that have come to frequent the habitations of man and animals, but we must also know the intimate life histories of all those groups of insects that may possibly bring about the contamination of food by disease organisms. Down to the present, discoveries of transmission have been *followed* by more or less active biological work on the vectors. How much better it would have been had this work prophetically been done *before*. There is no excuse for delay in the prosecution of this important work.

(4) Here and there practically all over the world there are men—principally medical men, it must be confessed —working on such problems of medical entomology as are at hand and can be studied most easily. The total output of these isolated workers is surprising. As I put it in an address recently delivered before the American Public Health Association at Buffalo, "A glance through any recent number of the *Review of Applied Entomology* or the *Tropical Diseases Bulletin* shows that a volume of work of this kind is going on that must be really appalling to the bibliographer." But most of this work is done on individual initiative. It is not correlated. The results are not readily available except for the reviews just mentioned and their like or from some recently published book, or as with mosquitoes, from my annual reports to the New Jersey association on the mosquito work of the world. All workers everywhere must be kept absolutely up to date. No time must be lost in duplication of investigations, except for that much of duplication which

is necessary for confirmation or for testing of results in different climatic regions.

(5) We now come to the fifth great need—a centralized foundation or institute for medical entomology. If the four needs which we have briefly touched are admitted, then we can meet them most efficiently through well-endowed centralized foundation. It is true that admirable work will go on without such a foundation. Schools of tropical medicine all over the world will continue to foster research work. More medical colleges and more of the great universities will take up the teaching of medical entomology and will train future research men. And research laboratories will eventually be established in such institutions.

But we will get speedier and sounder results from an institution established for the especial promotion of this kind of research, to support a competent corps of workers who may be placed in exactly the right places geographically and who may work absolutely unhampered for lack of any facility that can be supplied by money, to correlate the work of these and of all others, and to keep workers of all nations thoroughly up to date with all that is going on.

With such an institution properly administered, it is easy to see that the problems of medical entomology will be in the way of being solved in the shortest possible time and that the ideal situation will be reached comparatively soon when the world will have exact biological information about the groups of insects which will doubtless be convicted of the carriage of disease in time now rapidly approaching.

HORMONE CONTROL OF CYCLIC GROWTH AND FUNCTION OF THE FEMALE GENITAL ORGANS[1]

DR. EDGAR ALLEN

THIS paper attempts a brief survey of some experimental results with an active substance which is probably the principal female sex hormone. The purpose is not to review the recent literature,[2] but merely to summarize certain results of which the writer has first-hand information.

Growth of the female genital organs is cumulative up to the time of the attainment of puberty. From this time throughout sexual maturity, growth and accelerated function of the genital organs recur periodically or become cyclic. In non-pregnant mammals these cyclic changes can be described in simplest terms as alternating periods of growth and regression in the genital tract and mammary glands. Associated with the growth phase follicles approach maturity in the ovaries. When the follicles are largest preliminary to ovulation, the lower mammals show signs of intense sexual activity. In female mammals other than primates mating reactions are limited to this time (oestrus or "heat"). Toward the end of the oestrous period the follicles may rupture and extrude the mature ova at ovulation, or they may fail to reach full maturity, in which case they necessarily undergo atresia. In some mammals with short cycles the regressive phase sets in soon after a short oestrus, in others the growth phase may continue for varying inter-

[1] Read before a joint session of the sections of medicine and chemistry of the American Association for the Advancement of Science, Philadelphia, December, 1926. From the Department of Anatomy, University of Missouri School of Medicine.

[2] An extensive review is now in preparation in collaboration with Professor E. A. Doisy, of St. Louis University.

vals, to be followed later by regression. The regressive phase is marked by leucocytic infiltration of the uterus and vagina in lower mammals and by uterine hemorrhage in primates. In either case the return of the genital organs to a condition of relative quiescence is accomplished.

If pregnancy occurs these periodic changes of the non-pregnant cycle are replaced by the longer period of gestation. This is fundamentally a growth phase, at least as far as the uterus and mammary glands are concerned. Following birth of the young, involution of the uterus constitutes the regressive phase. This is paralleled by regression of the mammary glands in case lactation is not fulfilled.

At the close of sexual life (the menopause in primates) a final gradual retrogression of the sex organs is associated with progressive atresia of the ovaries.

These growth changes in the genital organs during the non-pregnant cycle are caused by a hormone from the ovaries. Ample evidence from removal of ovaries has established this point. A considerable amount of evidence has been presented by earlier investigators to show that certain extracts of ovaries and placenta contain this growth-inducing principle. Among these earlier contributions the work of the following should be cited: Lane-Claypon and Starling (1906), Iscovesco (1912), Fellner (1912) (1913), Aschner (1913), Okintschitz (1914), Hermann (1915) and Frank and Rosenbloom (1915). The early work was handicapped by the use of a difficult test for activity of injected extracts—the reaction of the uterus. The internal location of this organ necessitated its removal for critical examination and required a new animal for each test. Furthermore, there was no very definite end point to this uterine reaction, making it difficult to apply the test quantitatively. Reviews of this field as late as 1923 reveal conflicting results and relatively few clear-cut demonstrations of hormonal function.

The large amounts of ovarian extracts in wide clinical use were not tested biologically (at least in this country) because there was no practicable method.

Following a histological study of conditions in the genital organs of the mouse during the various phases of the oestrous cycle the writer attempted, in collaboration with Dr. E. A. Doisy, of St. Louis University, to test the effects of ovarian extracts. It was found that the contents of follicles from pig ovaries, injected subcutaneously in rats from which the ovaries had previously been removed, caused the occurrence of typical oestrous changes in the genital tract. In the first series of experiments fresh liquor folliculi and emulsions of residues from alcoholic extracts returned positive tests. Three to six injections at intervals of four to six hours proved the most efficient dosage. As in the normal animals these changes could be detected by microscopic examination of the cells in the vaginal lumen. This made it possible to follow the action of the extracts at several periods during the course of the experiment without killing the test animals. Due to the short cycle in the mouse and rat (four to five days for both the growth and regressive phases) positive tests were apparent on the third day of the experiment. These positive reactions consisted of the finding of a single type of cell, non-nucleated, cornified epithelial scales, as the only components of the vaginal contents. The spayed control, or the test animal injected with an inactive fraction, showed a vaginal smear containing many polymorphonuclear leucocytes. These changes are so clear-cut as to be unmistakable and the same test animal can be used repeatedly. Furthermore, the reaction has a definite end point, making its use as a quantitative test possible.

Histological section of the genital organs of these test animals showed the growth changes induced by injections to be equivalent to the maximum changes which occur in normal animals under the influence of their own

ovaries. A completely new epithelial wall of the vagina was grown under the action of these extracts in the three days required for the reaction in the rat and mouse.

Rapid hyperplasia is also induced in the uterus, especially in the epithelial tissue lining the surface and in the glands. Active secretion, which in these animals is retained in the uterus by cervical constriction, distends the uterine horns to a translucent condition.

There is a corresponding wave of growth in the uterine tubes and mammary glands, but this action can be more clearly demonstrated in other animals.

After injections are discontinued the regressive phase sets in and much of the tissue resulting from the growth producing action of the injected hormone degenerates and is removed by leucocytic infiltration as in the normal animal.

This experimental oestrus in rats and mice can be induced by fresh liquor folliculi or lipoid extracts from the follicles of hen, cow, sheep, pig and human ovaries. Consequently it is not species specific.

Contrary to the work of several earlier investigators who used uterine reactions as a test, our experiments, and later those of Johnston and Gould (1926), with extracts of corpora lutea from pigs and cows returned negative results. These tests led us to the conclusion that the corpora lutea (developing in the ruptured ovarian follicles) of pigs and cows probably do not continue the secretion initiated by the follicles to any appreciable extent. Therefore the follicles are probably the principal ovarian source of the active substance in these animals.

Test animals in which experimental oestrous periods had been induced by injections of extracts apparently experienced mating instincts similar to normal animals in oestrus. Copulation was followed by formation of "vaginal plugs" of coagulated ejaculate as in normal rats and mice. Test rats and mice from which the ova-

ries have been removed and normal animals which are not in oestrus usually will not mate. Apparently then, in the final analysis, this hormone is largely responsible for the female instincts.

It seemed probable from these experiments that the follicular hormone might quite completely substitute for the endocrine function of the sexually mature ovary in these animals at least in the absence of pregnancy. This was interpreted to mean that a fluctuation in the amount of a single hormone, rather than the interaction of several, would quite adequately explain the necessary mechanism of the oestrous cycle.

Recently many papers have appeared in this field which greatly extend the experimental evidence bearing upon endocrine relations of the female sex organs. The following should be cited: Giesy (1920), Corner (1923) (1924), Fraenkel and Fonda (1923), Courrier (1924) (1925), Brouha and Simonet (1925), Burrows and Johnston (1925), Seckinger (1924), Dickens, Dodds and Wright (1925), Fellner (1925), Frank and Gustavson (1925), Hart *et al.* (1925), Hisaw (1925), Kennedy (1925), Steinach *et al.* (1925), Zondek *et al.* (1925) (1926), Collings (1926), Hartman, C. *et al.* (1926), Lacquer *et al.* (1926), Lipschutz (1926), Loewe (1926), Murphey *et al.* (1926), Papanicolaou (1926), Parkes (1926), Riddle (1926) and Smith, M. G. (1926). No adequate discussion of these can be undertaken in this paper.

Our next experiments[3] were designed to test the effects of this active substance on immature animals. Previous histological examination of ovaries of immature rats had shown the presence of many small and moderately well-developed follicles with relatively little interstitial tissue. These findings stressed the possibility that these partly developed follicles might be causative agents in prepubertal growth of the genital organs. To test this hypothesis several litters of animals taken just after

[3] In collaboration with Dr. Doisy (1924).

weaning, at ages between twenty-four and thirty days, were used. Series of injections lasting over two to five days were made. In the immature female rat and mouse there is normally no opening of the genital tract until the attainment of puberty—the outer portion of the vagina being composed of a solid cord of cells. Injected extracts of liquor folliculi caused an acceleration of growth in the vaginal epithelium to the point of cornification, and this resulted in the opening of the vaginal orifice considerably before it would otherwise have occurred. Parallel growth changes and active secretion were induced in the uterus. The conclusion indicated is that the hormone secreted by the follicular tissue of the immature ovary is probably responsible for the prepubertal growth of the genital organs. The possibility was also advanced that the same causative agent might be responsible for the development of the secondary sexual characters.

Using the reaction in the rat to test the activity of various chemical fractions a considerable chemical purification of this material has been accomplished by Dr. Doisy and others. Defining the rat unit as the least amount of active material which will give a full oestrous reaction in the spayed mature rat, he has been able to reduce this amount to as little as 0.007 mg of residue. Chemical analyses show that these residues contain C, H, N and P as about 92 per cent. of their total constituents.

Early in the course of our application of this new test of ovarian extracts experiments were tried with commercial preparations then being used in clinical cases. Uniformly negative tests resulted from the extracts prepared for injection. The preparations in tablet form to be taken by mouth were dissolved and extracted by the same method which gave positive results from liquor folliculi. These were also negative to this test. Our residues of extracts of liquor folliculi dissolved in oil,

which were positive when injected subcutaneously, were negative when administered in much larger amounts by stomach tube.

Series of injections of extract in much larger doses than required to cause oestrus in the spayed female had no effect upon spermatogenesis in the young male. The testes at the end of the series of injections could not be distinguished histologically from those of control litter brothers. All stages of active spermatogenesis were present in the testis tubules and large numbers of spermatozoa were present in the epididymis. If there is an antagonistic action of the female sex hormone for maleness, it apparently must act over a longer period of time than included in these experiments.

Early in the course of this work the opportunity arose to test extracts of cystic follicles from human ovaries.[4] These analyses have shown that the follicular hormone in considerable concentration is present in certain types of cystic disorders of the ovaries.

Later the opportunity arose to test other human genital tissues, in collaboration with Dr. J. P. Pratt, of the Henry Ford Hospital, Detroit, and Dr. Doisy. Dr. Pratt made collections of follicular fluid from normal follicles of human ovaries exposed at laparotomy, and also excised human corpora at various stages in the menstrual cycle. The hormone was found to be present in high concentration in normal follicles. Positive tests were also returned from corpora of both menstruation and pregnancy. As previously stated, these results were in marked contrast with the tests of extracts from corpora of pigs and cows. A continuation of these experiments should establish the range of hormone production by the ovary during the menstrual cycle.

Early in the course of experimental work positive tests had been obtained with extracts of human placentas at

[4] Specimens have been supplied by Drs. E. A. Graham, Q. U. Newell and F. P. McNalley, of Washington University School of Medicine, and by Dr. J. P. Pratt, of Henry Ford Hospital.

full term. As occasion offered human placentas recovered earlier in gestation were tested. Lastly, extracts of a human chorionic vesicle from an ectopic pregnancy of about forty to forty-five days which contained a 12.5 mm embryo gave positive results. These analyses furnished additional evidence for the conclusion that a similar hormone to that produced in the ovary was produced by embryonic membranes and placenta and in increasing amounts as gestation continued. The active material from the chorionic vesicle measured only a few mouse units. The yield from the human placenta at term may range as high as 420 rat units or even higher, the rat unit being at least six or eight times greater than the mouse unit. There is, however, a great deal of variation in yields of active substance from this source. But from the middle to the end of gestation the placenta contains more of this active substance than the ovaries. Since the corpus luteum may be excised from the ovary quite early in the gestation period and since growth of follicles is retarded during this time, it would seem probable that the placenta takes over this hormonal function of the ovary during pregnancy. Tests of tissues of pregnancy in other species have shown the presence of this material in the cotyledonary placentas of cows and the chorionic membranes of horses. Further tests of material from other species are being made.

Hartman's work upon reproduction in the opossum has shown this animal to be ideal for the study of mammary function, for all the mammary glands are grouped together in the pouch. This makes possible the determination of growth in these organs by palpation in the living animal. In collaboration with Hartman and Dupre a considerable amount of growth has been induced in the mammary glands and also in the other genital organs of spayed opossums by injected extracts of liquor folliculi and human placenta.

There are several differences between the oestrous cycles of lower mammals and the menstrual cycles of

primates which make the results obtained from lower animals of doubtful application to the menstrual cycle.[5] The most striking difference is the occurrence of menstruation in primates. No such process occurs in the lower mammals. The outstanding event of the oestrous cycle of the lower mammals is the limitation of sex instincts to the short period of oestrus, which occurs near the time of ovulation. At other times the female avoids sexual relations. In the menstrual cycle sex instincts seem to be more evenly diffused throughout the interval. What evidence we have points to ovulation near the middle of the interval between menses, the cycle being dated from the first appearance of menstrual bleeding.

Earlier work by Heape, Van Herwerden and Corner has shown that monkeys have a typical menstrual cycle. In addition to the usual human menstrual phenomena there is marked reddening and swelling of the cutaneous regions surrounding the external genitalia.

Therefore, experiments were designed to test the effects of injections of extracts upon monkeys.[6] As substitution of extracts for ovarian function was desired it was necessary to remove ovaries from these animals. In the course of this work some data bearing upon the main problem were obtained.

Previous to operation observations were made upon normal animals for several months to obtain individual histories of sexual activity. In two cases at the time of removal of the ovaries recently ruptured follicles were noticed with a distention of the corresponding fallopian tubes. By injecting normal saline solution into the tubes two unfertilized ova were recovered, one on the tenth day, the other on the fourteenth day, following the first appearance of the previous menses. Together with an unfertilized tubal ovum and a degenerating uterine

[5] The contrast in hormone content of corpora lutea from cows and pigs with that of human beings has already been mentioned.

[6] In press. This work in monkeys was assisted by grants from the Committee for Research in Problems of Sex of the National Research Council.

ovum recovered by Corner on the fourteenth and seventeenth days, respectively, these quite definitely established the time of ovulation, if it does occur during the cycle in question, in the latter half of the second week of the menstrual cycle.

Serial sections were made of both ovaries from each of six animals. Histological study of these ovaries showed a complete absence of corpora lutea in two animals in which a total of fifteen menstrual cycles had been observed previous to ovariectomy. This is conclusive proof that ovulation had not occurred. In a third animal only two corpora were found to account for four recorded menstrual periods. In the other animals enough corpora were observed to account for all observed menstrual cycles. These data supplement those published by Corner and establish definitely that ovulation may not necessarily occur during normal menstrual cycles. How, then, can an internal secretion from the corpus luteum be considered a necessary causal factor for menstrual phenomena?

In four animals the ovaries were removed either just after ovulation or toward the end of the follicular phase when large follicles were present in the ovaries. Removal of the ovaries at this stage of the cycle was followed by apparently typical menstrual bleeding. These operative menses began on the fourth to sixth days, following the removal of ovarian hormonal influence. The duration of these operative menses was longer and the flow more profuse than normal menses. Aspiration of the contents of a large follicle in one ovary of another animal had a similar effect. Therefore, the removal of the endocrine influence of the ovaries immediately after or toward the end of the follicular phase of the cycle resulted in an acceleration of the appearance of the following menses. In some cases the acceleration was estimated at as much as ten days. Following ovariectomy the reddening and swelling of the vulva and surrounding

regions disappeared; by the end of the second week after operation the skin of this region was white.

At the time of removal of the ovaries measurements were made of the size of each uterus. The animals were then left for periods sufficiently long for retrogression of the genital organs following ovariectomy. Then series of injections of active extracts, which had previously been standardized by tests in spayed rats, were injected. Two or three injections daily were given for periods ranging from nine to twenty days. The total number of rat units injected varied from 64 to 230. The first sign of activity of extracts was the appearance of reddening of the "sexual skin." This usually began before the seventh day of the experiments. Toward the end of the first week leucocytes began to disappear from the vaginal smear and there was a corresponding increase in the number of epithelial elements. Toward the end of a series of injections, partly or wholly cornified epithelial cells predominated. In seven of ten experiments bleeding followed the discontinuance of injections in from three to seven days. The duration of these experimental menses varied from one to three days. In one case intermittent bleeding for six days was observed. The flow was scanty but characteristic. No bleeding occurred during the period of injections and none followed three series in an animal from which the uterus had been removed.

In each animal before injections were begun, laporatomy was performed and control measurements taken of the uterus. At the end of series of injections experimental measurements were made of the same uterus before removal for histologic study. In one case an amount of growth equal to that found in the largest normal uterus just after ovulation was obtained. In the other four animals comparison with control measurements showed considerable increase in size.

Histological examination of experimental tissues showed growth in all genital tissues. The vaginal walls

were greatly thickened in the injected animals and growth to the point of cornification occurred in some cases. Another proof of rapid hyperplasia was the high incidence of cells dividing by mitoses in the germinal layers of the epithelium.

The cervices from experimental animals were considerably larger than the controls. Cervical glands showed growth to rather extreme coiling. Rapid hyperplasia was also evident in the uterine glands of the fundus, as many as four to six dividing cells being present in a single section of certain glands. There was some histological indication of secretion droplets along the outer border of the epithelium. Sections of the fimbria of the uterine tubes showed a high incidence of dividing cells indicating rapid growth of this epithelium also.

One mammary gland from each animal was excised as a control before beginning the series of injections. The second gland from the same animal was excised at the end of the experiment. Cross sections of the nipples showed a considerable thickening of the epidermis of the experimental gland. Flat mounts of the whole glands showed complete repair of castrate atrophy by growth of ducts and the budding off of new alveoli.

These experiments in monkeys led to the following conclusions: (1) This active substance served to induce growth processes in the whole female genital tract and mammary glands. (2) It also caused the secondary sexual changes of reddening and swelling of the skin about the external genital organs. (3) The decrease or temporary absence of hormone following cessation of injections allowed the degeneration of tissue built up as a result of this anabolic endocrine influence. (4) Menstruation seemed to be due to a decrease or temporary absence of this secretion after it had been acting for a certain time. (5) There is no necessity of a specific secretion of the corpus luteum as a causative agent in the menstrual cycle. In case ovulation does occur the

corpus may continue the secretion of the follicular hormone in primates. The resorption of material from atretic follicles or the persistence of cystic follicles, however, may possibly have a similar result. (6) Extracts of human placenta were as effective as those of follicles of pig ovaries. The continuance of availability of this hormone from the placenta throughout the gestation period would account for the absence of menstruation during pregnancy. More work is necessary to establish the wide range of this hormone in the placentas of several species.

The rat test previously described is now being used in the preparation of extracts by several biological manufacturing concerns. Material of considerable concentration[7] has been available for the past year for experimental use in clinical cases. The results of some preliminary clinical tests have been published by Dr. Pratt and others. It is probable that additional tests will establish the value of this hormone as a therapeutic agent in clinical medicine.

[7] Our tests of these preparations by Parke, Davis and by Squibb have confirmed their standardization.